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Effect of Acetazolamide on Visual Function in Patients With Idiopathic Intracranial Hypertension and Mild Visual Loss:

The Idiopathic Intracranial Hypertension Treatment Trial

The NORDIC Idiopathic Intracranial Hypertension Study Group Writing Committee

Abstract

IMPORTANCE—Acetazolamide is commonly used to treat idiopathic intracranial hypertension (IIH), but there is insufficient information to establish an evidence base for its use.

OBJECTIVE—To determine whether acetazolamide is beneficial in improving vision when added to a low-sodium weight reduction diet in patients with IIH and mild visual loss.

DESIGN, SETTING, AND PARTICIPANTS—Multicenter, randomized, double-masked, placebo-controlled study of acetazolamide in 165 participants with IIH and mild visual loss who received a low-sodium weight-reduction diet. Participants were enrolled at 38 academic and private practice sites in North America from March 2010 to November 2012 and followed up for 6 months (last visit in June 2013). All participants met the modified Dandy criteria for IIH and had a perimetric mean deviation (PMD) between −2 dB and −7 dB. The mean age was 29 years and all but 4 participants were women.

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INTERVENTIONS—Low-sodium weight-reduction diet plus the maximally tolerated dosage or acetazolamide (up to 4 g/d) or matching placebo for 6 months.

MAIN OUTCOMES AND MEASURES—The planned primary outcome variable was the change in PMD from baseline to month 6 in the most affected eye, as measured by Humphrey Field Analyzer. Perimetric mean deviation is a measure of global visual field loss (mean deviation from age-corrected normal values), with a range of 2 to −32 dB; larger negative values indicate greater vision loss. Secondary outcome variables included changes in papilledema grade, quality of life (Visual Function Questionnaire 25 [VFQ-25] and 36-Item Short Form Health Survey), headache disability, and weight at month 6.

RESULTS—The mean improvement in PMD was greater with acetazolamide (1.43 dB, from −3.53 dB at baseline to −2.10 dB at month 6; n = 86) than with placebo (0.71 dB, from −3.53 dB to −2.82 dB;n = 79); the difference was 0.71 dB (95% CI, 0 to 1.43 dB; *P*= .050). Mean improvements in papilledema grade (acetazolamide: −1.31, from 2.76 to 1.45; placebo: −0.61, from 2.76 to 2.15; treatment effect, −0.70; 95% CI, −0.99 to −0.41; *P* < .001) and vision-related quality of life as measured by the National Eye Institute VFQ-25 (acetazolamide: 8.33, from 82.97 to 91.30; placebo: 1.98, from 82.97 to 84.95; treatment effect, 6.35; 95% CI, 2.22 to 10.47; *P* = . 003) and its 10-item neuro-ophthalmic supplement (acetazolamide: 9.82, from 75.45 to 85.27; placebo: 1.59, from 75.45 to 77.04; treatment effect, 8.23; 95% CI, 3.89 to 12.56; *P* < .001) were also observed with acetazolamide. Participants assigned to acetazolamide also experienced a reduction in weight (acetazolamide: −7.50 kg, from 107.72 kg to 100.22 kg; placebo: −3.45 kg, from 107.72 kg to 104.27 kg; treatment effect, −4.05 kg, 95% CI, −6.27 to −1.83 kg; *P* < .001).

CONCLUSIONS AND RELEVANCE—In patients with IIH and mild visual loss, the use of acetazolamide with a low-sodium weight-reduction diet compared with diet alone resulted in modest improvement in visual field function. The clinical importance of this improvement remains to be determined.

Idiopathic intracranial hypertension (IIH) is a disorder primarily of overweight women of childbearing age, characterized by increased intracranial pressure with its associated signs and symptoms, including debilitating headaches and vision loss in an alert and oriented patient. Neuroimaging and cerebrospinal fluid (CSF) analysis results are normal except for increased intracranial pressure. Also, no secondary cause of intracranial hypertension is apparent. The above features compose the modified Dandy criteria for IIH (eTable 1 in the Supplement).[1]

Treatment with weight-loss intervention in uncontrolled studies appears to be important, with as little as 6% reduction reported to be effective.[2,3] Surgical treatments have evolved from subtemporal decompression[4] to CSF shunting procedures[5,6] and optic nerve sheath fenestration.[7,8] Pharmacologic therapies for IIH began with the 1961 article by Paterson et al[9] reporting beneficial results with corticosteroids. Long-term adverse effects and rebound intracranial hypertension limit their use. Jefferson and Clark[10] treated 30 patients with various diuretics and reported improvement in symptoms and signs.

Lubow and Kuhr[11] reported a series of patients with IIH, many of whom were treated successfully with acetazolamide and weight reduction. Data on the dosage of acetazolamide, however, are based on limited experience. Gücer and Viernstein[12] used intracranial pressure

monitoring and showed gradual CSF pressure reduction in patients receiving acetazolamide once they reached a dosage of 4 g/d. These studies were uncontrolled, and to our knowledge there are no properly designed clinical trials to guide therapy in IIH.[13]

Because the efficacy of pharmacologic therapy has not been adequately studied, the Neuro-Ophthalmology Research Disease Investigator Consortium (NORDIC) IIH Study Group developed the Idiopathic Intracranial Hypertension Treatment Trial, a multicenter, double-masked, randomized, placebo-controlled study of acetazolamide in participants with mild visual loss. All participants received a lifestyle modification program that focused on weight reduction with a low-sodium diet because this intervention is widely accepted in practice and there was no equipoise regarding its use. The purpose of the trial was to determine the effect of acetazolamide in reducing or reversing visual loss after 6 months of treatment when added to a weight-reduction program.[14]

Methods

Participants

The study was approved by the institutional review board at each site and individual written informed consent was obtained. eTable 2 in the Supplement outlines the major eligibility criteria for the Idiopathic Intracranial Hypertension Treatment Trial. Participants aged 18–60 years were eligible if they met the modified Dandy criteria (eTable 1 in the Supplement)[1] and had reproducible mild visual loss (−2 to −7 dB perimetric mean deviation [PMD]). We chose an upper limit of −2 dB so that participants would have some room to improve; −7 dB was chosen as a lower limit to maintain clinical equipoise because enough investigators believed that surgical treatments were necessary for participants with more severe visual loss. Participants needed to have bilateral papilledema, have an elevated CSF opening pressure, be untreated with regard to IIH, and have no secondary cause of increased intracranial pressure present; other entry criteria are found in eTable 2 in the Supplement.

Randomization and Masking

Participants were enrolled at 38 sites in North America from March 2010 to November 2012, with follow-up ending in June 2013. They were randomly assigned to receive a supervised diet either with acetazolamide or with matching placebo. Randomization was stratified by site and included blocking to ensure balance among the treatment groups within a site after every 4 participants had been enrolled at that site. The only individuals with access to the treatment assignments during the trial before database lock were an unmasked programmer who generated the randomization plan, an unmasked statistician who served as a liaison with the independent data and safety monitoring board, and unmasked staff responsible for packaging and labeling of study drug. These individuals did not communicate with any other staff involved in the trial about study-related matters. Further details concerning randomization and masking are presented in the eMethods in the Supplement.

Intervention

A specific dietary plan and lifestyle modification program was offered to all study participants through the New York Obesity Nutrition Research Center; this is described in the eMethods in the Supplement.

The study drug was acetazolamide (250 mg) or matching placebo tablets. The initial dosage of study drug was 4 tablets daily in 2 divided doses, followed by dosage increases of 1 tablet every week up to a maximum dosage of 4 g/d for participants receiving acetazolamide. We chose this maximum dosage because increasing dosages of acetazolamide with concomitant intracranial pressure monitoring showed gradual CSF pressure reduction once participants reached a dosage of 4 g/d.[12] The dosage escalation was stopped if the participant's papilledema grade (Frisén scale)[15,16] became less than 1 in both eyes and the PMD improved to equal to or better than −1 dB in each eye, unless the presence of other symptoms such as headache or pulse synchronous tinnitus suggested that the dosage escalation continue. Participants who were unable to tolerate the study drug could gradually decrease the dosage to a minimum of one-half tablet daily. Participants who discontinued study drug continued to be followed up, if willing, for the planned 6-month duration.

Treatment failure was defined when a participant with baseline PMD up to −3.5 dB had visual function worsen by more than 2 dB PMD from baseline in either eye, or when a participant with baseline PMD between −3.5 dB and −7 dB had visual function worsen by more than 3 dB PMD from baseline in either eye, confirmed by a second perimetric examination. An adjudication committee, using all available clinical information, needed to confirm that the worsening was most likely due to uncontrolled intracranial pressure and progression of IIH. Participants who experienced treatment failure were withdrawn from further participation in the trial and referred to their physicians for further treatment.

Evaluations

Participants had visits at screening, baseline, and 1, 2, 3, 4.5, and 6 months after baseline. Evaluations performed at screening and baseline included a medical history and physical and neurologic examinations, urine pregnancy test, vital signs, complete blood cell count and blood chemistry panel with electrolyte levels, and an ophthalmologic examination. Magnetic resonance imaging was performed within 2 months of enrollment, and a diagnostic lumbar puncture was performed, including opening pressure measurement and CSF cell count, glucose, and protein measurements. Race and ethnicity information, with categories defined using National Institutes of Health guidelines, was obtained by the investigator during the screening process in consultation with the participant.

Participants had automated perimetry in both eyes with Humphrey Field Analyzer SITA Standard program 24-2. The testing was performed by a technician certified by the Visual Field Reading Center. Each participant had at least 2 initial visual field examinations conducted at least 30 minutes apart. Because removal of spinal fluid may temporarily improve visual function in IIH, we required at least 1 visual field examination to be conducted after the lumbar puncture and for the participant to have 2 visual field

examinations whose results for PMD and shape of defects were in agreement. The 2 PMD measurements at baseline were averaged.

The papilledema grade (Frisén scale)[15,16] was documented by the Photographic Reading Center with fundus photographs and by the site investigator; values range from 0 (normal) to 5 (severe papilledema). A best corrected visual acuity, using trial lenses mounted in spectacles, was measured with Early Treatment of Diabetic Retinopathy Study charts. Vision-related quality of life was assessed with the National Eye Institute Visual Function Questionnaire 25 (VFQ-25) and its 10-item neuro-ophthalmic supplement[17,18]; a 4- to 6-point change in VFQ-25 scores is clinically meaningful.[19] Generic health-related quality of life was assessed with the 36-Item Short Form Health Survey.[20] Quality-of-life scores range from 0 to 100, with higher scores indicating better quality of life. The 6-item Headache Impact Test (HIT-6) Inventory[21] was used to assess headache effect; scores range from 36 to 78, with higher scores indicating worse headache severity.

Assessment of vital signs, ophthalmologic examination, visual acuity testing, perimetry, and papilledema evaluation were performed at each follow-up visit. The blood chemistry panel result was obtained at months 1, 2, 3, and 6 and the complete blood cell count was obtained at months 3 and 6. The quality-of-life questionnaire and HIT-6 Inventory results were obtained at month 6. All participants were encouraged to have a second lumbar puncture for CSF pressure measurement at month 6.

Outcome Variables

The primary outcome variable was the change in PMD from baseline to month 6 in the eye with the most severe visual loss at baseline (study eye). With standard automated perimetry, stimulus light intensity is defined on a logarithmic scale in decibel units. The perimeters used in the study estimated light intensity thresholds at 54 test locations over a 50-dB range (10 000-0.1 asb [apostilbs, a measure of light intensity]) within the central 21 degrees of the visual field. Perimetric mean deviation, a summary statistic of overall visual field loss, was calculated by the perimeter software (Humphrey Statpac; Zeiss Humphrey Systems). The normal range varies with age, with the 95th percentile falling between −1 and −2 dB. Secondary outcome variables included changes from baseline to month 6 in PMD in the eye with the least severe visual loss at baseline (fellow eye), papilledema grade, CSF pressure, visual acuity (number of correct letters), quality of life and HIT-6 Inventory outcomes, weight, vital signs, and laboratory test results. Additional secondary outcome variables, determined at month 6, included presence of headache and treatment failure. Adverse events and laboratory test abnormalities were also examined.

Sample Size Determination

Preliminary data from the NORDIC IIH Study Group were used to estimate the standard deviation of the primary outcome variable, 6-month change in PMD. Data on changes in PMD during a period of 6.4 months (SD, 1.9 months) were available for 37 patients with mild visual loss (−2 dB to −7 dB). In the most affected eye, the mean change in PMD was 0.82 dB (SD, 2.35 dB). Under the assumption of a standard deviation of 2.35 dB, an initial sample size of 140 participants (70 per group) was chosen to provide90% power to detect a

group difference in mean change of 1.3 dB, using a *t* test and a significance level of 5% (2-tailed). This was increased to 154 participants (77 per group) to account for an anticipated withdrawal rate of approximately 10%. Monitoring of the withdrawal rate during the trial revealed this rate to be higher than anticipated, and the final sample size was inflated to 165 participants. Justification for the chosen effect size of 1.3 dB is provided in the eMethods in the Supplement.

Statistical Analysis

The primary analyses were performed according to the intention-to-treat principle (with the exception that follow-up ceased for participants experiencing treatment failure) and included all available data from all randomized participants. The primary statistical analysis used an analysis of covariance model with treatment group as the factor of interest, center as a stratification factor, and baseline PMD and papilledema grade in the study eye as covariates. This model was used to compare the adjusted treatment group means (*t* test) and to determine a 95% CI for the adjusted treatment group difference in mean response (treatment effect) at month 6. Missing data were accommodated in the analysis with multiple imputation. Details concerning the multiple imputation algorithm are provided in the eMethods. A significance level of 5% (2-tailed) was used for hypothesis testing.

A secondary analysis of the primary outcome variable used a repeated-measures analysis of covariance model (ie, the so-called mixed model repeated measures [MMRM] analysis strategy[22]) that included treatment group as the factor of interest, center as a stratification factor, and baseline PMD and papilledema grade in the study eye as covariates. The model also included terms for visit (categorical), the interaction between baseline PMD and visit, and the interaction between treatment group and visit. The covariance matrix for the within-subject observations was modeled with an unstructured pattern. A third analysis was performed that was identical to the primary analysis but carried forward the last observed PMD value for participants who reached the end point of treatment failure.

A prespecified analysis of the PMD outcome was performed that included all eyes (study eyes and fellow eyes) that satisfied the criterion of having a baseline value between −2 dB and −7 dB. An MMRM strategy of analysis was used as in the secondary analysis of the primary outcome variable, except that it also accommodated nonzero correlation between the within-subject outcomes for the study and fellow eyes.

Interactions between treatment group and selected baseline variables (age, race, baseline PMD in the study eye, papilledema grade in the study eye, weight change in the previous 6 months, and constant visual loss) were examined separately for the primary outcome variable by adding the appropriate main effect and interaction terms to the statistical model, using the MMRM analysis strategy.

Continuous secondary outcome variables for efficacy were analyzed in a manner similar to that for the primary outcome variable, using analysis of covariance and multiple imputation to accommodate missing data. The baseline value of the outcome variable was used as a covariate in the statistical model instead of the baseline PMD. Vital signs, weight, and laboratory test results were analyzed with the MMRM analysis strategy but did not include

adjustment for center. Because of the large amount of missing data at month 6 for CSF pressure, this was analyzed with analysis of covariance, adjusting for the baseline value with no imputation for missing data. For presence of headache, a logistic regression model was used to assess treatment effects. This model included treatment group as the factor of interest and baseline PMD and the baseline value of the outcome variable as covariates. Missing data were accommodated with a multiple imputation algorithm described in the eMethods in the Supplement.

Further details concerning the statistical analyses can be found in the eMethods, including a mediation analysis of the primary outcome variable to determine the degree to which the effect of acetazolamide on PMD was mediated by its effect on weight. The mediation analysis was performed with Mplus version 5.2. All other statistical analyses used SAS version 9.3.

Results

We enrolled 161 women and 4 men. Their average age was 29 years (range, 18–52 years). The baseline characteristics were comparable in the 2 treatment groups (Table 1); additional baseline information is published elsewhere.[23] Participant disposition is summarized in Figure 1. Sixty-nine of the 86 participants (80%) in the acetazolamide group completed follow-up compared with 57 of the 79 participants (72%) in the placebo group. Sixteen participants in each treatment group withdrew from the trial, mainly because of loss to follow-up and time commitment problems (Figure 1). There were 7 participants who reached the end point of treatment failure in the trial, 6 in the placebo group and 1 in the acetazolamide group ($P = .06$). Ten participants permanently discontinued the study drug during the trial, 9 in the acetazolamide group (7 of whom completed follow-up) and 1 in the placebo group (who completed follow-up). Eight of the drug discontinuations were due to adverse events, and the other 2 (both in the acetazolamide group) were due to pregnancy and the desire to become pregnant.

Both treatment groups experienced improvement in PMD over time in the study eye (Figure 2), with the mean improvement in the acetazolamide group being significantly larger than that in the placebo group at month 6 (acetazolamide: 1.43 dB, from −3.53 dB at baseline to −2.10 dB at month 6; placebo: 0.71 dB, from −3.53 dB at baseline to −2.82 dB at month 6; treatment effect, 0.71 dB; 95% CI, 0 to 1.43 dB; $P = .050$) (Table 2). Secondary analyses of the primary outcome variable using different strategies for accommodating missing data yielded similar results (Table 2). Perimetric mean deviation in the fellow eye also improved with acetazolamide treatment at month 6 (acetazolamide: 0.87 dB, from −2.28 dB to −1.41 dB; placebo: 0.42 dB, from −2.28 dB to −1.86 dB; treatment effect, 0.44 dB; 95% CI, 0.01 to 0.87 dB; $P = .045$) (Table 3). An analysis that included all eyes that had a PMD between −2 dB and −7 dB at baseline (165 study eyes and 96 fellow eyes) also yielded a significant effect of acetazolamide at month 6 (acetazolamide: 1.47 dB, from −3.33 dB to −1.86 dB; placebo: 0.81 dB, from −3.33 dB to −2.52 dB; treatment effect, 0.66 dB; 95% CI, 0.16 to 1.17 dB; $P = .01$).

The treatment effect on the primary outcome variable was substantially greater in participants with a baseline papilledema grade of 3–5 (2.27 dB) than in those with a baseline papilledema grade of 1–2 (−0.67 dB) (eTable 3 in the Supplement).

There was significant improvement in Frisén papilledema grade associated with acetazolamide treatment in the study eye and in the fellow eye for both the fundus photography and site investigator ratings (Table 3). Acetazolamide-treated participants also experienced significant improvement in quality-of-life measures, including the VFQ-25 total score (acetazolamide: 8.33, from 82.97 to 91.30; placebo: 1.98, from 82.97 to 84.95; treatment effect, 6.35; 95% CI, 2.22 to 10.47; $P = .003$) and its 10-item neuro-ophthalmic supplement (acetazolamide: 9.82, from 75.45 to 85.27; placebo: 1.59, from 75.45 to 77.04; treatment effect, 8.23; 95% CI, 3.89 to 12.56; $P < .001$), as well as the 36-Item Short Form Health Survey Physical Component Summary and Mental Component Summary scores (Table 3). No significant treatment effects were noted with respect to headache disability (HIT-6 total score) or visual acuity (Table 3). At month 6, headaches were reported by 69% of participants in the acetazolamide group and 68% of participants in the placebo group (adjusted odds ratio, 1.10; 95% CI, 0.53 to 2.28; $P = .80$).

Only 85 participants (47 [55%] in the acetazolamide group and 38 [48%] in the placebo group) agreed to a lumbar puncture at month 6. The adjusted mean change in CSF pressure was −112.3 mm H_2O (from 357.2 mm H_2O at baseline to 244.9 mm H_2O at month 6) in the acetazolamide group and −52.4 mm H_2O (from 357.2 mm H_2O at baseline to 304.8 mm H_2O at month 6) in the placebo group (treatment effect, −59.9 mm H_2O; 95% CI, −96.4 to −23.4 mm H_2O; $P = .002$). Participants receiving acetazolamide lost more weight during 6 months (mean, −7.50 kg, from 107.72 kg to 100.22 kg) than those receiving placebo (mean, −3.45 kg, from 107.72 kg to 104.27 kg) (treatment effect, −4.05 kg; 95% CI, −6.27 to −1.83 kg; $P < .001$) (eTable 4 in the Supplement). Acetazolamide also led to reductions in waist circumference and systolic and diastolic blood pressure (eTable 4). In the mediation analysis, the total effect of acetazolamide on PMD in the study eye was estimated to be 0.75 dB (95% CI, 0.06 to 1.44 dB; $P = .03$), with the direct effect being 0.72 dB (95% CI, 0.02 to 1.42 dB; $P = .04$) and the indirect effect (that mediated through the effect on weight) being only 0.03 dB (95% CI, −0.10 to 0.16 dB; $P = .64$).

Adverse events that occurred in greater than 5% of study participants are summarized in Table 4. Events that occurred significantly more frequently in the acetazolamide group included paresthesia, dysgeusia, fatigue, decreased carbon dioxide level, nausea, vomiting, diarrhea, and tinnitus. Nine participants had adverse events that were classified as serious. Three of the participants were in the placebo group, 2 of whom experienced rapidly failing vision requiring hospitalization and treatment with optic nerve sheath fenestration (both declared to have reached the end point of treatment failure) and another who was hospitalized with pneumonia. In the acetazolamide group, the 6 events included hospitalizations for renal impairment, transaminitis, elevated lipase with pancreatitis, and diverticulitis. The other 2 serious adverse events included an allergic reaction of unknown origin and hypokalemia. As expected, acetazolamide-treated participants had a marked decrease in mean carbon dioxide level and a marked increase in mean chloride level compared with placebo-treated participants (eTable 5 in the Supplement). A mild decrease

in mean potassium level was also observed with acetazolamide but did not require potassium supplementation in any participants. No significant changes in sodium levels or in liver function test results were apparent with acetazolamide, except for the case noted above.

Average adherence (as measured by counts of dispensed and returned pills) was 89% (SD, 19%) in the acetazolamide group and 93% (SD, 14%)in the placebo group. The mean dosage of study medication that participants were receiving at the conclusion of their participation was 2.5 g (SD, 1.5 g) in the acetazolamide group and 3.5 g (SD, 1.1 g) in the placebo group. More detailed information on each participant's final dosage is provided in eTable 6 in the Supplement.

Discussion

This is the first multicenter, double-blind, randomized, controlled clinical trial, to our knowledge, to show that acetazolamide improves visual outcome in IIH. Our results apply to participants with mild visual loss defined as having a PMD from −2 to −7 dB. They also apply in the setting of a concurrent low-sodium weight reduction diet.

The treatment effect on PMD was 2.94 dB greater in participants with a papilledema grade greater than or equal to 3 at baseline (2.27 dB) than in those with lower grades (−0.67 dB), which may be due to more affected eyes having more capacity for improvement with acetazolamide treatment; the differential treatment effect was more apparent for subgroups defined by papilledema grade than for those defined by PMD in the study eye. It might also relate to improved visual function and improved axoplasmic flow.

Acetazolamide treatment was also associated with a significant reduction in papilledema grade. Papilledema can improve by a reduction in CSF pressure or by loss of optic nerve axons. It is not likely that the latter occurred in many cases because few participants had worsening of their visual field status.

We found acetazolamide-associated improvements in quality-of-life measures. The VFQ-25 total score and its 10-item neuro-ophthalmic supplement and the 36-Item Short Form Health Survey Physical Component Summary and Mental Component Summary scores all significantly improved. Suñer et al[19] showed that a 4- to 6-point change in VFQ-25 score represents a clinically meaningful change corresponding to a 15-letter change in best corrected visual acuity. Thus, the mean 6.4-point improvement with acetazolamide appears to represent clinically meaningful improvement.

Clinical improvement in IIH has been reported to be associated with an approximately 6% weight loss.[3] Idiopathic Intracranial Hypertension Treatment Trial participants in both the placebo group (3.45 kg) and the acetazolamide group (7.50 kg) lost weight, with the group difference being 4.05 kg. Our mediation analysis demonstrated that the benefit of acetazolamide on PMD was not via its effect on weight.

Acetazolamide is thought to work by inhibition of carbonic anhydrase that causes a reduction in transport of sodium ions across the choroid plexus epithelium. It has been

shown to reduce CSF production in humans by 6% to 50%.[24] This inhibition appears to require a higher dosage than is routinely used.[12]

There were few unexpected adverse events associated with acetazolamide use. No participant, to our knowledge, experienced permanent morbidity from receiving acetazolamide. A larger number of participants discontinued acetazolamide use during the trial (9) than discontinued placebo (1), most because of adverse events. Although serum sodium level remained unchanged in both groups, a mild decrease in serum potassium level was found (0.23 mmol/L;95% CI,0.12 to 0.34; $P < .001$), but participants did not require potassium supplementation as a result, similar to findings from another report.[25] There were 2 cases of renal stones (both in the acetazolamide group). There was 1 case of transaminitis and 1 case of pancreatitis in the acetazolamide group; each resolved with discontinuation of acetazolamide.

A limitation of our study is the 19% withdrawal rate, although the frequency of and reasons for withdrawal were similar in the 2 treatment groups. This rate may be due, in part, to the intensity of the visit schedule. More participants receiving acetazolamide than placebo discontinued treatment, most of whom completed follow-up, which may have attenuated the estimated treatment effect. Another limitation is the difficulty in the interpretation of the estimated treatment effect on PMD. Our chosen minimal clinically important difference for PMD was 1.3 dB and was based on a small pilot study designed to estimate the level of decibels at which a clinician makes a decision to change therapy (see eMethods in the Supplement) and did not incorporate patient experience or input. Our estimated treatment effect was only approximately half of this value. Although the beneficial effects of acetazolamide on secondary outcome variables such as papilledema grade and vision-related quality of life support the clinical relevance of its effect on PMD, further research is needed to discern the functional significance of a particular decibel improvement in PMD to a patient.

Conclusions

In patients with IIH and mild visual loss, the use of acetazolamide with alow-sodium weigh treduction diet, compared with diet alone, resulted in modest improvement in visual field function. The clinical importance of this improvement remains to be determined.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Glossary

CSF	cerebrospinal fluid
IIH	idiopathic intracranial hypertension
MMRM	mixed model repeated measures
PMD	perimetric mean deviation

Appendix

Authors/Writing Committee: The following investigators of the NORDIC Idiopathic Intracranial Hypertension Study Group take authorship responsibility for the study results: Michael Wall, MD; Michael P. McDermott, PhD; Karl D. Kieburtz, MD, MPH; James J. Corbett, MD; Steven E. Feldon, MD; Deborah I. Friedman, MD, MPH; David M. Katz, MD; John L. Keltner, MD; Eleanor B. Schron, PhD; Mark J. Kupersmith, MD.

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Role of the Sponsors: A representative of the sponsor (NEI), Eleanor Schron, PhD, served on the steering committee. Also, the NEI appointed a data and safety monitoring board (DSMB) to monitor participant safety and oversee study conduct and progress. DSMB members were independent academic leaders who received funding from NEI for their DSMB service. The NEI required DSMB review and approval of the manuscript before submission. The NEI had no other role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

The steering committee members contributed to management, analysis, and interpretation of the data and the preparation, editing, and review of the manuscript. The sites contributed to data collection, and compensation was received for patient care. Others contributed to the study design, methods, conduct and procedures; their efforts were supported by NIH grant U10 EY017281.

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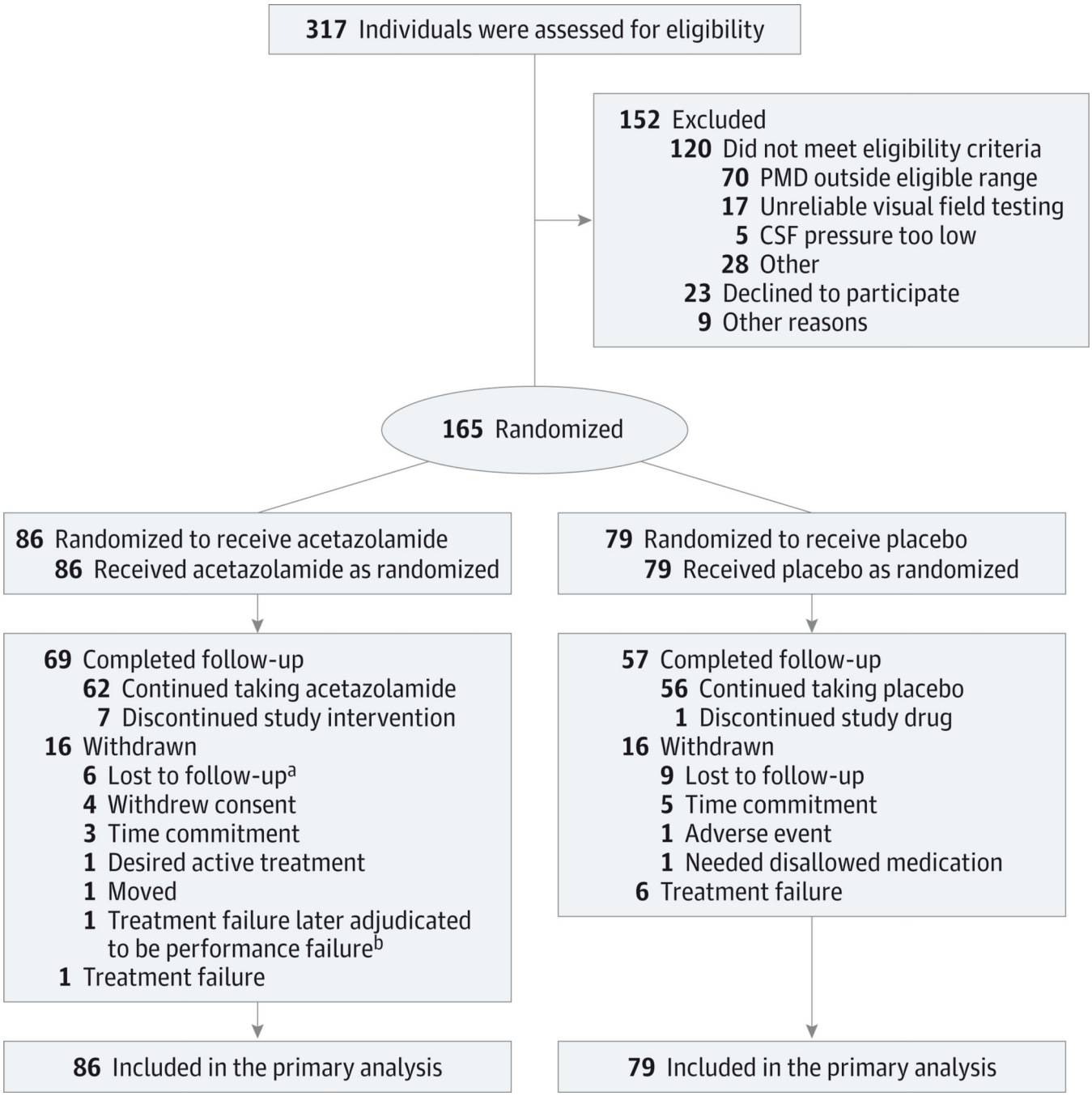
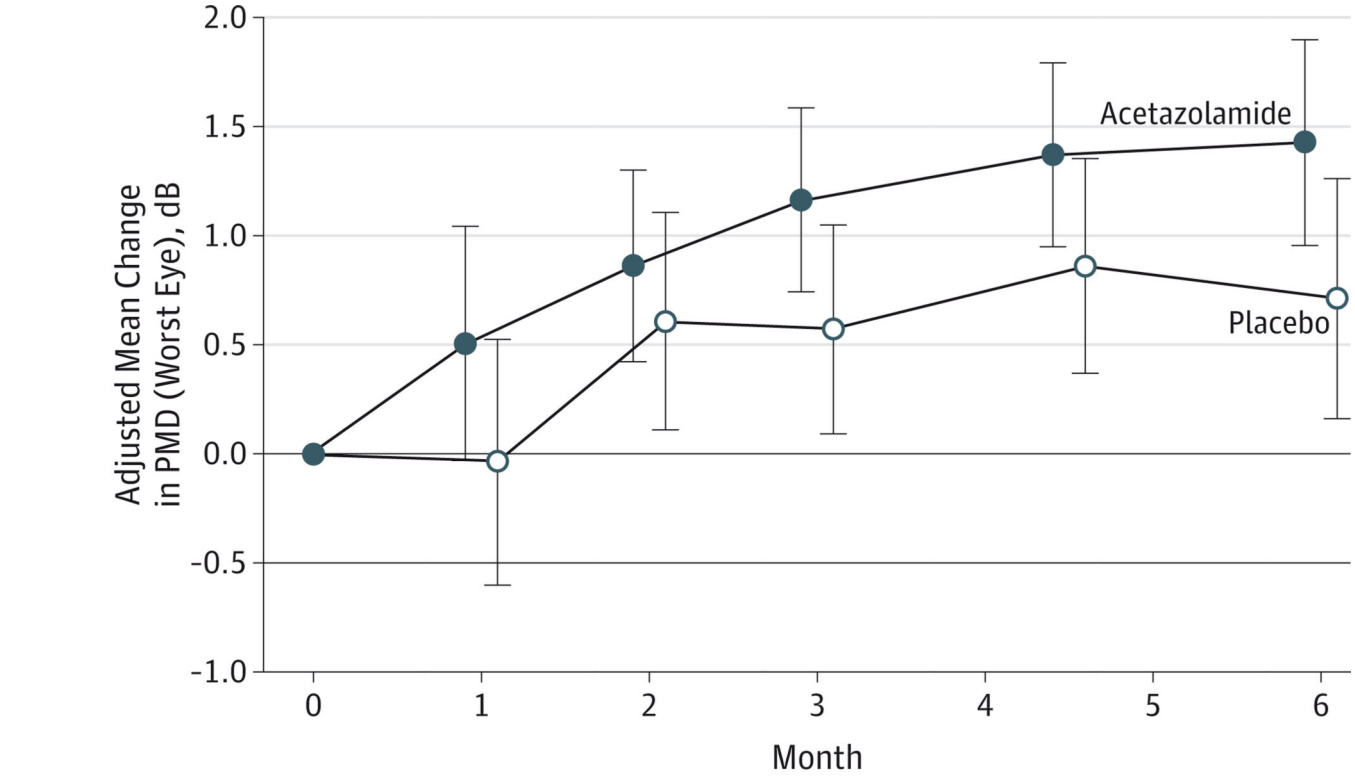


Figure 1.

Participant Disposition and Flow Through the Trial (CONSORT Diagram)

[a]Two participants who were lost to follow-up had previously discontinued the study intervention.

[b]A performance failure is a worsening of perimetry test results due to lack of effort, attention, or concentration characterized by examination inconsistencies and unreproducible results.



No. of patients						
Acetazolamide	86	82	76	76	67	70
Placebo	79	73	67	60	60	59

Figure 2.

Adjusted Mean Change in Perimetric Mean Deviation (PMD) Over Time by Treatment Group

Numbers of patients reflect those contributing PMD data in each group at each time point. The adjusted means were obtained from an analysis of covariance model that included center, baseline papilledema grade (study eye), and baseline PMD as covariates. Missing data were accommodated with multiple imputation. Bars around the adjusted group means indicate 95% CIs. Adjusted group means for each treatment group are slightly offset around each visit to avoid overlap.

Table 1

Baseline Characteristics by Treatment Group

Variable	No. (%)	
	Acetazolamide (n = 86)	Placebo (n = 79)
Age, mean (SD), y	28.2 (6.9)	30.0 (8.0)
Female sex	84 (97.7)	77 (97.5)
Race		
White	54 (62.8)	54 (68.4)
Black	25 (29.1)	16 (20.3)
Mixed/other	4 (4.6)	2 (2.5)
Not reported	3 (3.5)	7 (8.9)
Weight, mean (SD), kg	108.1 (25.6)	107.3 (24.5)
Body mass index, mean (SD)[a]	40.0 (8.5)	39.9 (8.1)
Weight change in the past 6 mo, mean (SD), kg	10.7 (16.7)	8.8 (16.9)
Transient visual obscurations	55 (63.9)	57 (72.1)
Diplopia	20 (23.3)	16 (20.2)
Constant visual loss	25 (29.1)	28 (35.4)
Photophobia	42 (48.8)	37 (46.8)
Headache	70 (81.4)	69 (87.3)
Pulsatile tinnitus	45 (52.3)	41 (51.9)
Perimetric mean deviation, mean (SD), dB		
Study eye	−3.5 (1.2)	−3.5 (1.1)
Fellow eye	−2.3 (1.1)	−2.3 (1.1)
Papilledema grade (fundus photography)[b]		
Study eye		
1	8 (9.3)	12 (15.2)
2	32 (37.2)	23 (29.1)
3	20 (23.3)	20 (25.3)
4	24 (27.9)	21 (26.6)
5	2 (2.3)	3 (3.8)
Fellow eye		
1	15 (17.4)	14 (17.7)
2	33 (38.4)	28 (35.4)
3	19 (22.1)	21 (26.6)
4	19 (22.1)	14 (17.7)
5	0	2 (2.5)
Visual acuity (No. of correct letters), mean (SD)		
Study eye	56.8 (5.1)	55.6 (5.9)
Fellow eye	58.3 (4.3)	56.2 (6.4)

Variable	No. (%)	
	Acetazolamide (n = 86)	Placebo (n = 79)
HIT-6 total score, mean (SD)[c]	60.3 (8.7)	59.1 (9.3)
CSF pressure, mean (SD), mm H_2O	348.9 (94.1)	342.0 (70.7)
VFQ-25, mean (SD)[c]		
Total score	83.8 (14.1)	82.1 (13.4)
10-item neuro-ophthalmic supplement total score	75.8 (15.4)	75.0 (13.7)
SF-36 component summary score, mean (SD)[c]		
Physical	45.4 (9.8)	46.3 (8.2)
Mental	45.2 (11.8)	44.0 (13.3)

Abbreviations: CSF, cerebrospinal fluid; HIT-6, 6-Item Headache Impact Test; SF-36, 36-Item Short Form Health Survey; VFQ, Visual Function Questionnaire.

[a] Body mass index is calculated as weight in kilograms divided by height in meters squared.

[b] Frisén papilledema grade is an ordinal scale that uses ocular fundus features to rate the severity of papilledema; grade 0 indicates no features of papilledema and grade 5 indicates severe papilledema.

[c] Score ranges are as follows: HIT-6 total score: 36–78 (higher scores indicate greater headache severity); VFQ-25 total score, VFQ-25 10-item neuro-ophthalmic supplement total score, and SF-36 summary scores: 0–100 (higher scores indicate better quality of life).

Table 2

Treatment Effects on the Primary Outcome Variable, Change From Baseline to Month6 in Perimetric Mean Deviation (PMD) in the Study Eye

	Adjusted Mean (SE), dB[a]		Treatment Effect (95% CI)	*P* Value
	Acetazolamide	Placebo		
Missing data accommodated with multiple imputation				
Baseline to month 6	−3.53 (0.09) to −2.10 (0.24)	−3.53 (0.09) to −2.82 (0.09 to 0.28)		
Change	1.43 (0.24)	0.71 (0.28)	0.71 (0 to 1.43)	.050
Missing data accommodated with MMRM				
Baseline to month 6	−3.53 (0.09) to −2.02 (0.24)	−3.53 (0.09) to −2.89 (0.26)		
Change	1.51 (0.24)	0.64 (0.26)	0.87 (0.19 to 1.56)	.01
Missing data accommodated with multiple imputation except LOCF imputation used for treatment failures				
Baseline to month 6	−3.53 (0.09) to −2.06 (0.29)	−3.53 (0.09) to −3.25 (0.30)		
Change	1.47 (0.29)	0.28 (0.30)	1.19 (0.34 to 2.05)	.007

Abbreviations: LOCF, last observation carried forward; MMRM, mixed model repeated measures.

[a]Values are mean changes (in decibels) from baseline to month 6 in PMD in the study eye, adjusted for center, baseline PMD in the study eye, and baseline papilledema grade in the study eye.

Table 3

Treatment Effects on Secondary Outcome Variables

Variable	Adjusted Mean (SE)[a]		Treatment Effect (95% CI)	*P* Value
	Acetazolamide	Placebo		
PMD, fellow eye, dB				
Baseline to month 6	−2.28 (0.09) to −1.41 (0.15)	−2.28 (0.09) to −1.86 (0.17)		
Change	0.87 (0.15)	0.42 (0.17)	0.44 (0.01 to 0.87)	.045
Papilledema grade (fundus photography)				
Study eye				
Baseline to month 6	2.76 (0.08) to 1.45 (0.11)	2.76 (0.08) to 2.15 (0.11)		
Change	−1.31 (0.11)	−0.61 (0.11)	−0.70 (−1.00 to −0.40)	<.001
Fellow eye				
Baseline to month 6	2.50 (0.08) to 1.36 (0.10)	2.50 (0.08) to 1.98 (0.10)		
Change	−1.14 (0.10)	−0.52 (0.11)	−0.62 (−0.91 to −0.32)	<.001
Papilledema grade (site investigator rating)				
Study eye				
Baseline to month 6	2.60 (0.09) to 0.85 (0.13)	2.60 (0.09) to 1.75 (0.14)		
Change	−1.75 (0.13)	−0.85 (0.14)	−0.91 (−1.27 to −0.54)	<.001
Fellow eye				
Baseline to month 6	2.32 (0.09) to 0.68 (0.11)	2.32 (0.09) to 1.56 (0.12)		
Change	−1.64 (0.11)	−0.76 (0.12)	−0.88 (−1.19 to −0.58)	<.001
VFQ-25				
Total score				
Baseline to month 6	82.97 (1.08) to 91.30 (1.47)	82.97 (1.08) to 84.95 (1.53)		
Change	8.33 (1.47)	1.98 (1.53)	6.35 (2.22 to 10.47)	.003
10-Item neuroophthalmic supplement				
Baseline to month 6	75.45 (1.14) to 85.27 (1.55)	75.45 (1.14) to 77.04 (1.62)		
Change	9.82 (1.55)	1.59 (1.62)	8.23 (3.89 to 12.56)	<.001
SF-36				
PCS				
Baseline to month 6	45.82 (0.70) to 51.66 (1.01)	45.82 (0.70) to 48.64 (1.03)		
Change	5.84 (1.01)	2.82 (1.03)	3.02 (0.34 to 5.70)	.03
MCS				
Baseline to month 6	44.61 (0.98) to 50.23 (1.16)	44.61 (0.98) to 46.78 (1.16)		
Change	5.62 (1.16)	2.17 (1.17)	3.45 (0.35 to 6.55)	.03
HIT-6 total score				
Baseline to month 6	59.70 (0.70) to 50.14 (1.05)	59.70 (0.70) to 50.59 (1.14)		
Change	−9.56 (1.05)	−9.11 (1.14)	−0.45 (−3.50 to 2.60)	.77
Visual acuity				

Variable	Adjusted Mean (SE)[a]		Treatment Effect (95% CI)	*P* Value
	Acetazolamide	Placebo		
Study eye				
Baseline to month 6	56.26 (0.43) to 58.91 (0.49)	56.26 (0.43) to 58.90 (0.49)		
Change	2.65 (0.49)	2.64 (0.51)	0.01 (−1.45 to 1.46)	.99
Fellow eye				
Baseline to month 6	57.28 (0.43) to 59.38 (0.49)	57.28 (0.43) to 59.01 (0.51)		
Change	2.10 (0.49)	1.73 (0.51)	0.37 (−1.17 to 1.90)	.64

Abbreviations: MCS, Mental Component Summary; PCS, Physical Component Summary; PMD, perimetric mean deviation; SF-36, 36-Item Short Form Health Survey; VFQ, Visual Function Questionnaire.

[a]Values are mean changes from baseline to month 6, adjusted for center, the baseline value of the outcome variable, and baseline papilledema grade in the study eye.

Table 4

Adverse Events by Treatment Group[a]

	Acetazolamide (n = 86)		Placebo (n = 79)		
Event	**Participants, No. (%)**	**Events, No.**	**Participants, No. (%)**	**Events, No.**	***P* Value[b]**
Elevated ALT	6 (7.0)	6	3 (3.8)	4	.50
Decreased CO_2	9 (10.5)	9	0	0	.003
Diarrhea	12 (14.0)	14	3 (3.8)	4	.03
Dizziness	8 (9.3)	11	3 (3.8)	4	.22
Dysgeusia	13 (15.1)	13	0	0	<.001
Dyspepsia	7 (8.1)	8	1 (1.3)	1	.07
Dyspnea	7 (8.1)	8	2 (2.5)	2	.17
Fatigue	14 (16.3)	16	1 (1.3)	1	<.001
Headache	13 (15.1)	17	11 (13.9)	16	>.99
Nasopharyngitis	5 (5.8)	6	8 (10.1)	11	.39
Nausea	26 (30.2)	30	10 (12.7)	10	.008
Paresthesia	41 (47.7)	51	5 (6.3)	6	<.001
Post-LP syndrome	5 (5.8)	9	6 (7.6)	9	.76
Rash	7 (8.1)	8	2 (2.5)	2	.17
Sinusitis	3 (3.5)	3	6 (7.6)	7	.31
Tinnitus	11 (12.8)	12	3 (3.8)	3	.05
Vomiting	12 (14.0)	13	3 (3.8)	3	.03

Abbreviations: ALT, alanine aminotransferase; LP, lumbar puncture.

[a] Values reported are the numbers (percentages) of participants experiencing the event at least once after the baseline visit; total numbers of events are also provided. Events occurring in at least 5% of study participants are listed.

[b] From Fisher exact test comparing the treatment groups with respect to the percentage of participants experiencing the event at least once after the baseline visit.