Supplementary Online Content

The NORDIC Idiopathic Intracranial Hypertension Study Group Writing Committee. Effect of acetazolamide on visual function in patients with idiopathic intracranial hypertension and mild visual loss: the Idiopathic Intracranial Hypertension Treatment trial

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. Methods, Statistical Analysis

Methods

Randomization: Randomization was stratified by site and included blocking to ensure balance among the treatment groups within a site after every four participants had been enrolled at that site. A programmer in the Data Coordination and Biostatistics Center (DCBC) generated the randomization plan, which was sent to the Clinical Materials Services Unit (CMSU) at the University of Rochester so that they could pre-code the study medication with the appropriate randomization numbers and distribute this medication to the sites. The order of assignment of the randomization numbers within each site was provided to a masked DCBC information analyst so that this information could be incorporated in the web-based enrollment module. A back-up system was in place whereby sites could call the DCBC to randomize a participant manually if necessary. The only individuals with access to the treatment assignments during the trial prior to database lock were the unmasked programmer in the DCBC who generated the randomization plan, an unmasked statistician in the DCBC who served as a liaison with the independent Data and Safety Monitoring Board, and unmasked staff at the CMSU. These individuals did not communicate with any other staff involved in the trial about study-related matters.

Site Personnel and Masking: Site personnel included a site principal investigator (PI), treating sub-investigator (TSI), site coordinator, visual field technician(s) and fundus photographer(s). The site PI screened potential participants and determined their eligibility. All site personnel were masked to the study drug assignment. After randomization, all inquiries pertaining to the study drug and adverse events were directed to the site coordinator and TSI to minimize possible bias of the site PI to the treatment assignment. The site PI was responsible for assessing the participants for possible treatment failure. All laboratory data incurred after the screening process were reviewed by the TSI.

Dietary Plan and Lifestyle Modification Program: A specific dietary plan and lifestyle modification program was offered to all study participants through the New York Obesity Nutrition Research Center. The intervention covered all three disciplines of weight loss and lifestyle modification (i.e., nutrition, physical activity, and behavior). All participants were assigned to a weight loss coach with weekly telephone communication. Further details of the dietary intervention have been published elsewhere[1]. The target goal for weight loss was 6% of baseline body weight.

Statistical Analysis

Multiple Imputation: Missing data for normally distributed outcome variables were accommodated in the analyses using multiple imputation. This was applied using a regression-based imputation model[2]. For participants with complete data up to a particular visit, a multiple regression model was fit that included the outcome at that visit as the dependent variable and outcomes at previous visits, treatment group, center, and papilledema grade as independent variables. Separate models were similarly constructed for each visit. Using these regression models, a missing value for a participant at a particular visit was imputed as a draw from the predictive distribution given the outcomes at previous visits (some possibly imputed), treatment group, center, and papilledema grade of the participant. This was done sequentially starting with the baseline visit and ending with the Month 6 visit. This process was repeated 100 times, resulting in 100 complete analysis data sets. The analyses were performed separately for each of the 100 complete analysis data sets, and the results were combined into one multiple imputation inference (estimated treatment effect and associated confidence interval and p-value)[2,3]. This approach is appropriate for data sets that have a monotone missing data pattern. When the data set did not precisely have this pattern, the monotone data augmentation method using Markov-Chain Monte-Carlo[4,5] was employed to impute the small amount of missing data that was required to make the missing data pattern monotone before applying the multiple imputation algorithm described above. For the dichotomous presence of headache outcome, if a participant was missing a response at a particular visit, missing data were imputed using a multiple imputation algorithm similar to that used for the primary outcome variable, but based on logistic regression[6]. For this outcome variable, center was not included in the imputation model, nor in the model used for the statistical analysis.

Mediation Analysis: A mediation analysis of the primary outcome variable was performed to determine the degree to which the effect of acetazolamide on PMD was mediated by its effect on weight. This analysis was performed using a multilevel structural equation model for the outcome of change from baseline in PMD in the worst eye[7-9].

The hypothesized mediator was the change from baseline in weight. The model for weight change included treatment, baseline weight, visit (categorical), the interaction between baseline weight and visit, and the interaction between treatment group and visit. The model for PMD change included treatment, baseline PMD, weight change (mediator), visit (categorical), the interaction between baseline PMD and visit, and the interaction between treatment group and visit. The effects of treatment on both weight change and PMD change were thus allowed to vary over time, but the association between weight change and PMD change was assumed to be the same at each visit; models that relaxed this assumption were found to fit more poorly than the original model specified here. Similar to the MMRM strategy for analysis of the individual PMD change and weight change outcomes, maximum likelihood was used for parameter estimation in the mediation model, accommodating missing data under the missing at random (MAR) assumption.

Choice of Effect Size: The effect size of 1.3 dB was chosen on the basis of a pilot study conducted prior to the trial as it reflected the minimal difference associated with a clinically significant change in the visual field. Twenty-five charts of IIH patients with mild visual loss who had at least five longitudinal visual field examinations were identified. Each of three readers reviewed all visual fields masked to the PMD associated with the field. The criterion for a clinically significant change in the field was *a priori* defined as a change from the index examination, confirmed on two consecutive subsequent examinations, which in the opinion of the reader would require a change in therapy for the patient. Agreement among at least two of the three participating readers was required for a change to be deemed clinically significant; in fact, all three readers were in agreement for 23 of the 25 patients. A clinically significant change was identified in 19 of the 25 patients. At the end of this process, the PMD associated with each visual field was obtained from the patient records. The minimal change in PMD that best discriminated between those who did and did not have a clinically significant change in their visual field examination was estimated using receiver operating characteristic (ROC) curve analysis. This analysis revealed that a change of 1.3 dB yielded a sensitivity of 79% (i.e., 15/19 patients who had a clinically significant change also had a change in PMD of > 1.3 dB) and a specificity of 83% (i.e., 5/6 patients who did not have a clinically significant change also had a change in PMD of ≤ 1.3 dB).

eTable 1. Modified Dandy Criteria

1. Presence of signs and symptoms of increased intracranial pressure
2. Absence of localizing findings on neurologic examination except those known to occur from increased intracranial pressure
3. Absence of deformity, displacement, or obstruction of the ventricular system and otherwise normal neurodiagnostic studies, except for evidence of increased cerebrospinal fluid pressure (> 200 mm H_2O). Abnormal neuroimaging except for empty sella turcica, optic nerve sheath with filled out CSF spaces, and smooth-walled non flow-related venous sinus stenosis or collapse should lead to another diagnosis
4. Awake and alert patient
5. No other cause of increased intracranial pressure present

Modified from Smith[10]

eTable 2. Major eligibility criteria for the IIHTT

Inclusion criteria

1. Diagnosis of IIH by modified Dandy criteria (eTable 1)
2. Age 18 to 60 years at time of diagnosis
3. Reproducible visual loss present on automated perimetry
4. Average perimetric MD -2 dB to -7 dB in the in eye with greatest loss
5. Opening CSF pressure > 250 mm H_2O or pressure of 200 to 250 mm H_2O and at least one of the following:
   - Pulse synchronous tinnitus
   - VI palsy
   - Grade II papilledema
   - Echography for drusen negative and no other optic disc anomalies mimicking disc edema present
   - Magnetic resonance venogram with lateral sinus collapse/stenosis
   - Partially empty sella on coronal or sagittal views and optic nerve sheaths with filled out CSF spaces next to the globe on T2 weighted axial scans
6. Presence of bilateral papilledema

Exclusion criteria

1. Total treatment of IIH of more than two weeks (except for acetazolamide which is limited to 1 week). For every day on treatment there must be a one-day washout period
2. Previous surgery for IIH including optic nerve sheath fenestration, CSF shunting procedures, subtemporal decompression and venous stenting
3. Previous gastric bypass surgery
4. Abnormal CSF contents
5. Other disorders causing visual loss
6. Optic disc drusen on exam or in previous history
7. Presence of diagnosed untreated obstructive sleep apnea
8. Exposure to a drug, substance or disorder that has been associated with elevation of intracranial pressure within 2 months of diagnosis such as lithium, vitamin A, or various cyclines
9. Other condition requiring diuretics, steroids or other pressure lowering agents including topiramate
10. Pregnancy or unwillingness for participant of childbearing potential to use contraception during the first year of the study

eTable 3. Treatment effects in subgroups on the primary outcome variable, change from baseline to Month 6 in PMD in the study eye

Variable	Treatment Group	Baseline *	Month 6 *	6-Month Change *	Treatment Effect (dB)	95% CI	P-value†
Age							
≤ 30 (n = 110)	ACZ (n = 61)	-3.57 (0.11)	-2.11 (0.29)	1.46 (0.29)	1.04	(0.17, 1.90)	
	Placebo (n = 49)	-3.57 (0.11)	-3.15 (0.34)	0.42 (0.34)			0.69
> 30 (n = 55)	ACZ (n = 25)	-3.45 (0.14)	-1.77 (0.46)	1.68 (0.46)	0.73	(-0.47, 1.94)	
	Placebo (n = 30)	-3.45 (0.14)	-2.50 (0.41)	0.95 (0.41)			
Race							
Caucasian (n = 108)	ACZ (n = 54)	-3.48 (0.10)	-1.97 (0.34)	1.51 (0.34)	0.78	(-0.10, 1.67)	
	Placebo (n = 54)	-3.48 (0.10)	-2.76 (0.35)	0.72 (0.35)			0.55
African-American (n = 41)	ACZ (n = 25)	-3.62 (0.19)	-1.96 (0.49)	1.66 (0.49)	1.34	(-0.25, 2.93)	
	Placebo (n = 16)	-3.62 (0.19)	-3.30 (0.65)	0.32 (0.65)			
Baseline PMD, study eye							
≥ -3.5 (n = 92)	ACZ (n = 48)	-2.70 (0.04)	-1.38 (0.34)	1.32 (0.34)	1.29	(0.30, 2.28)	
	Placebo (n = 44)	-2.70 (0.04)	-2.67 (0.38)	0.03 (0.38)			0.22
< -3.5 (n = 73)	ACZ (n = 38)	-4.58 (0.09)	-2.88 (0.39)	1.70 (0.39)	0.35	(-0.76, 1.46)	
	Placebo (n = 35)	-4.58 (0.09)	-3.23 (0.41)	1.35 (0.41)			
Baseline papilledema grade (fundus photography), study eye							
1-2 (n = 75)	ACZ (n = 40)	-3.59 (0.14)	-2.65 (0.35)	0.94 (0.35)	-0.67	(-1.66, 0.32)	
	Placebo (n = 35)	-3.59 (0.14)	-1.98 (0.37)	1.61 (0.37)			< 0.001
3-5 (n = 90)	ACZ (n = 46)	-3.48 (0.11)	-1.48 (0.33)	2.00 (0.33)	2.27	(1.32, 3.22)	
	Placebo (n = 44)	-3.48 (0.11)	-3.75 (0.35)	-0.27 (0.35)			
Weight change in 6 months prior to baseline							
Weight loss/no change (n = 90)	ACZ (n = 47)	-3.70 (0.13)	-2.32 (0.33)	1.38 (0.33)	0.57	(-0.36, 1.50)	
	Placebo (n = 43)	-3.70 (0.13)	-2.89 (0.35)	0.81 (0.35)			0.34
Weight gain (n = 75)	ACZ (n = 39)	-3.33 (0.11)	-1.65 (0.39)	1.68 (0.39)	1.27	(0.21, 2.33)	
	Placebo (n = 36)	-3.33 (0.11)	-2.92 (0.41)	0.41 (0.41)			
Constant visual loss at baseline							
No (n = 112)	ACZ (n = 61)	-3.41 (0.10)	-1.93 (0.28)	1.48 (0.28)	0.81	(-0.05, 1.68)	
	Placebo (n = 51)	-3.41 (0.10)	-2.75 (0.33)	0.66 (0.33)			0.81
Yes (n = 53)	ACZ (n = 25)	-3.78 (0.15)	-2.13 (0.46)	1.65 (0.46)	1.00	(-0.22, 2.22)	
	Placebo (n = 28)	-3.78 (0.15)	-3.13 (0.44)	0.65 (0.44)			

CI = Confidence interval; PMD = Perimetric mean deviation

* Values are means (standard errors) at baseline and Month 6, as well as mean changes from baseline to Month 6, in PMD in the study eye (in dB) adjusted for center, baseline PMD in the study eye, and baseline papilledema grade in the study eye. The statistical model also included terms for subgroup and the treatment by subgroup interaction.

† P-value for a test of the null hypothesis of no interaction between treatment group and the subgroup variable, i.e., for a test of the null hypothesis of equality of treatment effects in the two subgroups

eTable 4. Treatment effects on anthropometric and vital sign outcomes

	Adjusted Mean Change (SE) † (Baseline to Month 6)				
Variable	**ACZ**	**Placebo**	**Treatment Effect**	**95% CI**	**P-value**
Weight (kg)	-7.50 (0.76) (107.72 [1.95] to 100.22 [0.76])	-3.45 (0.83) (107.72 [1.95] to 104.27 [0.83])	-4.05	(-6.27, -1.83)	< 0.001
Body mass index	-3.29 (0.43) (39.93 [0.64] to 36.64 [0.43])	-1.26 (0.49) (39.93 [0.64] to 38.67 [0.49])	-2.02	(-3.31, -0.73)	0.002
Waist circumference (cm)	-8.56 (1.11) (111.54 [1.46] to 102.98 [1.11])	-3.89 (1.22) (111.54 [1.46] to 107.65 [1.22])	-4.67	(-7.93, -1.42)	0.005
Systolic BP (mmHg)	-7.67 (1.31) (124.01 [1.07] to 116.34 [1.31])	-3.00 (1.44) (124.01 [1.07] to 121.01 [1.44])	-4.67	(-8.52, -0.82)	0.02
Diastolic BP (mmHg)	-5.14 (1.03) (77.93 [0.87] to 72.79 [1.03])	-0.09 (1.13) (77.93 [0.87] to 77.84 [1.13])	-5.04	(-8.08, -2.01)	0.001
Pulse (beats/min)	-2.07 (1.32) (75.84 [0.79] to 73.77 [1.32])	-1.50 (1.47) (75.84 [0.79] to 74.34 [1.47])	-0.56	(-4.48, 3.35)	0.78

† Values are mean changes from baseline to Month 6 adjusted for the baseline value of the outcome variable. Values in parentheses are standard errors and the adjusted means (standard errors) at baseline and Month 6.

SE = Standard error; ACZ = Acetazolamide; CI = Confidence interval; BP = Blood pressure

eTable 5. Treatment effects on laboratory test results

	Adjusted Mean Change (SE) † (Baseline to Month 6)				
Variable	**ACZ**	**Placebo**	**Treatment Effect**	**95% CI**	**P-value**
Sodium (mmol/L)	0.10 (0.20) (138.99 [0.17] to 138.89 [0.20])	0.04 (0.22) (138.99 [0.17] to 138.95 [0.22])	0.06	(-0.53, 0.66)	0.84
Potassium (mmol/L)	-0.23 (0.04) (4.10 [0.02] to 3.87 [0.04])	0.00 (0.04) (4.10 [0.02] to 4.10 [0.04])	-0.23	(-0.34, -0.12)	< 0.001
Chloride (mmol/L)	3.72 (0.42) (102.81 [0.19] to 106.53 [0.42])	0.15 (0.45) (102.81 [0.19] to 102.96 [0.45])	3.57	(2.36, 4.79)	< 0.001
Carbon Dioxide (mmol/L)	-4.27 (0.44) (24.36 [0.22] to 20.09 [0.44])	-0.37 (0.47) (24.36 [0.22] to 23.99 [0.47])	-3.90	(-5.18, -2.62)	< 0.001
AST (U/L)	-3.04 (2.09) (23.41 [0.76] to 20.37 [2.09])	1.88 (2.27) (23.41 [0.76] to 25.29 [2.27])	-4.92	(-11.03, 1.19)	0.11
ALT (U/L)	-4.78 (1.91) (25.04 [1.33] to 20.26 [1.91])	-0.25 (2.08) (25.04 [1.33] to 24.79 [2.08])	-4.53	(-10.11, 1.04)	0.11
RBC (10^6/μL)	-0.02 (0.04) (4.64 [0.03] to 4.62 [0.04])	0.05 (0.04) (4.64 [0.03] to 4.69 [0.04])	-0.07	(-0.18, 0.03)	0.17
WBC (10^3/μL)	0.06 (0.26) (8.12 [0.16] to 8.18 [0.26])	-0.30 (0.27) (8.12 [0.16] to 7.82 [0.27])	0.36	(-0.38, 1.10)	0.83

† Values are mean changes from baseline to Month 6 adjusted for the baseline value of the outcome variable. Values in parentheses are standard errors and the adjusted means (standard errors) at baseline and Month 6.

SE = Standard error; ACZ = Acetazolamide; CI = Confidence interval; AST = Aspartate transaminase; ALT = Alanine transaminase; RBC = Red blood cell count; WBC = White blood cell count

eTable 6. Dosages of study medication at conclusion of study participation

Dosage (g)	Acetazolamide (n = 86)	Placebo (n = 79)
0.00-0.75	17 (19.8)	3 (2.5)
1.00-1.75	14 (16.3)	5 (5.1)
2.00-2.75	13 (15.1)	9 (13.9)
3.00-3.75	7 (8.1)	4 (5.1)
4.00	35 (40.7)	58 (73.4)

Values are numbers (percentages) of participants at each dosage

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