Effect of Acetazolamide on Visual Function in Patients with Idiopathic Intracranial Hypertension and Mild Visual Loss (The Idiopathic Intracranial Hypertension Treatment trial).

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Prior, smaller studies had shown the efficacy of weight loss as well as the potential efficacy of combined weight loss + acetazolamide (Diamox) for the management of vision loss in IIH. However, larger trials studying such therapies and additional trials assessing the appropriate dosage of acetazolamide for optimal vision improvement were lacking. Hence, the goal of this trial was to determine (on a larger scale) if acetazolamide + weight loss was effective in reducing or reversing vision loss in IIH.

Experimental design and statistics: This was a multi-center, double-blind, randomized, and placebo-controlled study. Eligible patient (18-60yrs old) had to meet the modified Dandy criteria for the diagnosis of IIH[1], and all patients were required to have reproducible, mild visual loss (-2 to -7 dB parametric mean deviation (PMD), which is based on the degree of VF loss on HVF testing; more (-) means more VF loss), bilateral papilledema, elevated CSF opening pressure, and no prior treatment for their IIH. All eligible and enrolled patients were exposed to a low-sodium, weight-reduction diet during the study. In addition, eligible patients were also randomized to receive either acetazolamide (250mg tablets) or placebo (matching dosage), along with their dietary intervention, over the course of the study. In the treatment group, the initial dose of acetazolamide was set at 500mg BID, with up-titration to a maximum, goal dose of 4000mg/day. Dosage escalation stopped once each participant's papilledema grade or PMD grade improved. If patients were ever unable to tolerate their respective dosage of acetazolamide, they were allowed to decrease their dosage down to a minimum of 125mg/day. The primary outcome was then the change in PMD from baseline to 6 months, in the eye with the most severe vision loss at baseline (i.e., the study eye). Examinations were conducted at baseline and then monthly until 6 months. This primary outcome was compared between treatment groups via an analysis of covariance, with baseline PMD and papilledema grade (among others) as covariates. Of note, this study only included patients with mild vision loss, as enough investigators felt that patients with more severe vision loss would be eligible for surgery. Therefore, the results of this trial were somewhat skewed towards those with less severe disease.

Results: In terms of baseline characteristics, both the acetazolamide group (N=86) and the placebo group (N=49) had a preponderance of females (> 97%) and a mean BMI of 40; other baseline characteristics were similar. A total of 20% of patients in the acetazolamide group were lost to follow-up, compared to 28% of patients in the placebo group. Of those who completed follow-up, more patients (N=7) discontinued treatment in the acetazolamide group as compared to the placebo group (N=1). While both treatment and placebo groups experienced an improvement in PMD in the study eye over time (Fig. 2), the mean improvement in the acetazolamide group was significantly larger than that in the placebo group (p=0.05). Further, the treatment effect was greater in patients with a higher, baseline level of papilledema (grade of 3-5) as compared to those with a lower baseline level of papilledema (grade of 1-2). The acetazolamide group also had a larger mean improvement in

[1] Modified Dandy Criteria: Presence of signs and symptoms of increased intracranial pressure; Absence of localizing findings on neurologic examination, except for those known to occur from increased intracranial pressure; Absence of deformity, displacement, or obstruction of the ventricular system and otherwise normal neurodiagnostic studies, other than evidence for increased cerebrospinal fluid opening pressure (>200 mm water); abnormal neuroimaging, other than 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; Awake and alert patient; No other cause of increased intracranial pressure present

papilledema grade. Finally, participants receiving acetazolamide lost more weight in the 6-month study period as compared to those receiving placebo (p<0.001), despite both groups being in a weight loss program. Through added statistical analyses, however, the study authors were able to attribute a greater percentage of vision improvement to an effect of acetazolamide, rather than to an effect of weight loss alone, in the acetazolamide group. For further secondary analyses that were performed in the study, see Table 3. For a summary of SEs related to acetazolamide, see Table 4 (paresthesias and nausea were the most frequently experienced). At the conclusion of the trial, the mean dosage of study medication was 2500mg/day in the acetazolamide group and 3500mg/day in the placebo group.

Conclusions: Overall, the results of this trial suggested that the use of acetazolamide + weight reduction was better than weight reduction and diet, alone, in improving vision in patients with IIH and mild vision loss. Notably, despite this, the data here did show that acetazolamide did little to improve headaches in these patients, as 69% of the acetazolamide group and 68% of the placebo group still reported headaches by the end of the study. This suggests that alternate therapies are likely needed for headaches associated with IIH, OR that patients with IIH may also have a super-imposed, primary headache disorder that warrants its own treatment regimen. Otherwise, a main limitation to the study was its enrollment of only patients with mild vision loss, and it is noteworthy that more participants in the acetazolamide treatment group discontinued treatment (as compared to placebo), so the study authors note that there may have been an undue influence of these factors on the observed treatment effect. However, at the time of publication, this was still a significant study, as it was the largest of its kind, and the first double-blind, placebo-controlled study to evaluate the efficacy of acetazolamide for patients with IIH and vision impairment.

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