Pseudotumor cerebri: What We Have Learned from the Idiopathic Intracranial Hypertension Treatment Trial

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ABSTRACT

Idiopathic intracranial hypertension, also known as pseudotumor cerebri, is an unexplained increase in intracranial pressure associated with permanent severe visual loss in 25% of cases and debilitating headaches. The condition is often associated with obesity. The Idiopathic Intracranial Hypertension Treatment Trial, a large, randomized, collaborative clinical trial, evaluated the efficacy of acetazolamide with weight loss versus placebo with weight loss in participants. Herein, we describe the major components of the clinical trial and discuss its shortcomings.

KEYWORDS: Idiopathic Intracranial Hypertension Treatment Trial, IIHTT, pseudotumor cerebri, papilledema, weight loss, visual field loss, perimetric mean deviation

INTRODUCTION

Idiopathic intracranial hypertension (IIH), also known as pseudotumor cerebri, is an unexplained increase in intracranial pressure that predominantly is a disease affecting women of child-bearing age who are overweight, but can arise from medication use or other conditions. Symptoms of IIH include transient visual obscuration, severe headache, diplopia from abducens (VI) nerve palsy, pulsatile tinnitus, and papilledema.1-5 Although acetazolamide combined with weight loss is a common treatment plan for IIH, the role and efficacy of acetazolamide are uncertain.5 Indeed, Johnson and colleagues found that 6% weight loss alone—which can be achieved within 3 to 6 months—will result in resolution of papilledema and IIH.1,6

The Idiopathic Intracranial Hypertension Treatment Trial (IIHTT) is the third in a series of large, randomized, collaborative clinical trials undertaken by the neuro-ophthalmology community.7-11 The IIHTT evaluated the efficacy of acetazolamide with weight loss (ACZ) versus placebo with weight loss (i.e., versus weight loss only [WLO]) among patients with mild visual field loss on automated perimetry. In this paper, we describe the major components of the IIHTT and evaluate the shortcomings of the trial.

THE IIHTT

A total of 165 participants with mild visual loss were enrolled in the IIHTT at 38 sites in North America. Eligibility criteria included age 18-60 years, reproducible visual field loss with a perimetric mean deviation (PMD) of -2 to -7 dB in the worst eye (study eye), a diagnosis of IIH by the modified Dandy criteria, and bilateral papilledema.7,10 Participants were randomized to initially receive 4 tablets daily in 2 doses of 250 mg acetazolamide or placebo, with the dosage increased by one tablet every 6 days with up to 16 tablets (4 grams) daily. All participants were also offered enrollment in a dietary and lifestyle modification program. The primary outcome variable was the mean change in visual field PMD at 6 months in the eye with worse visual loss.

In the trial, only the ACZ group achieved the target 6% weight loss. The PMD in the ACZ group improved by 1.43 dB at follow-up while the WLO group improved by 0.71 dB (P=0.050). The fellow eye in the ACZ group also demonstrated significant improvement in PMD at 0.87 dB as compared with WLO group at 0.42 dB (P=0.045). The papilledema grade significantly improved in both the study and fellow eyes in the ACZ group as compared with the WLO group using both fundus photography and site investigator ratings (p<0.001). Most quality-of-life measures were significantly higher for the ACZ group. The study concluded that acetazolamide with diet resulted in modest improvement in visual function than diet alone, but the clinical importance of the improvement remains to be determined.

SHORTCOMINGS OF THE IIHTT

The IIHTT was designed to determine the effectiveness of acetazolamide in reducing or reversing vision loss in IIH [pseudotumor cerebri] after 6 months of treatment. If both groups (ACZ, WLO) had achieved equivalent 6% weight loss, the effectiveness of acetazolamide could be obtained by subtracting the outcome of the WLO group from the ACZ group. However, the ACZ group, at 6.96% mean weight loss, had more than double the weight loss as compared with the WLO group at 0.71% mean weight loss for the WLO group. Less than 5% of the WLO group had 6% or more weight loss. Any attempt at comparing the ACZ group with the WLO group, in order to achieve the effectiveness of acetazolamide at this markedly unequal weight loss distribution, would be misleading and erroneous at best. Unfortunately, no amount of statistical arbitration or mediation will increase the over 95% of participants who did not achieve 6% weight loss in the WLO group. Hence, the IIHTT failed to demonstrate...
the effectiveness of acetazolamide in IIH at the targeted 6% weight loss. Because both groups (ACZ, WLO) did achieve 3% weight loss, the IIHTT would be able to assess the effectiveness of acetazolamide by comparing ACZ with WLO at 3% weight loss. Indeed, the IIHTT data showed better treatment outcome for the WLO group with 1.61 dB improvement (PMD: -3.59 dB initial; -2.65 dB 6-month) in comparison with ACZ with 0.94 dB improvement (PMD: -3.59 dB initial; -1.98 dB 6-month). This is in keeping with the findings of Johnson et al.14 which had documented a one-grade change in papilledema, i.e., resolution of mild papilledema [Frisén grades 1-2] with 3% weight loss.15 This may suggest that for mild papilledema, weight loss only without acetazolamide would be a reasonable treatment option, as only 3% weight loss is required.

It remains uncertain if acetazolamide is necessary if, through motivation, counseling and encouragement, a patient can achieve 6% weight loss.5,14 Clearly, the IIHTT participants achieved the desired 6% weight loss with use of acetazolamide, but at a price of significant adverse events. The IIHTT was only able to achieve 40% compliance of patients taking 4 grams of acetazolamide as patients developed adverse effects or there was noncompliance. In the IIHTT, acetazolamide was associated with a significantly greater rate of paresthesia, fatigue, dysgeusia, decreased carbon dioxide level, nausea, vomiting, diarrhea, and tinnitus. Serious adverse events in the ACZ group included hospitalization for renal impairment, transaminitis, elevated lipase with pancreatitis, diverticulitis, and one case of reduced blood count. Indeed, there have been case series reported of patients sustaining fatal aplastic anemia with acetazolamide use.16 Losing weight and maintaining weight loss are difficult challenges of our time.

UNANSWERED QUESTIONS ABOUT IIH

In addition to the uncertainty of obtaining optimal efficacy with acetazolamide and weight loss regimens, the pathophysiology of pseudotumor cerebri is yet to be determined. The design of IIHTT did not address causation in the development of pseudotumor cerebri. The proposed mechanisms of IIH pathophysiology are based on: 1) its propensity among obese females of child-bearing age; 2) its association with medications such as vitamin A and tetracycline; and 3) the absence of ventriculomegaly. Anatomic and hormonal etiologies have been considered.5,25 A filling defect within the venous sinuses may lead to IIH. Additionally, increased vitamin A or aldosterone may influence the development of IIH. Both estrogen and retinoic acid have been implicated in increasing resistance to CSF outflow by affecting epithelial membranes. Substances such as retinol-binding protein, aromatase, cytokines, and leptins secreted by adipose tissue may be involved in the pathophysiology of IIH and could explain the increased susceptibility among obese patients.24 The contribution of cerebral venous abnormalities such as the stenosis of the distal transverse cerebral sinuses or the formation of microthrombosis due to thrombophilia within the cerebral veins as a primal cause of IIH by increasing the resistance to CSF outflow is uncertain.2,5 The role of brain glymphatics in the pathophysiology of IIH remains to be explored.16,17 The IIHTT will examine potential selected biomarkers for IIH. Nonetheless, there are still many unanswered questions.

References

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