Letters

COMMENT & RESPONSE

Risk Index and Thrombolytic Treatment in Acute Ischemic Stroke

To the Editor In the article by Ovbiagele et al[1] published in *JAMA Neurology*—which tested the hypothesis that patients with stroke with a positive SPAN-100 index (the sum of a patient's age plus National Institutes of Health Stroke Scale of 100 or greater) selected from the Virtual International Stroke Trials Archive (VISTA) database might benefit from thrombolysis—the authors concluded that such SPAN-100–positive patients "should probably not be denied thrombolysis treatment on the basis of such a profile alone." Likewise they conclude that "the answer to the question posed about what to do regarding very elderly patients with very severe strokes…seems to be to treat them with intravenous thrombolysis…." They concluded this from finding that the SPAN-100 patients in their selection from the VISTA database treated with thrombolysis did better than those who did not receive that treatment (adjusted odds ratio, 0.46 [95% CI, 0.29-0.71]) The many limitations noted by the authors of querying the artificially created VISTA database are delineated and are very significant, yet do not seem to prevent the authors from making such treatment recommendations. This is also counter to the VISTA database founders stating that "[t]he VISTA database does not sanction reanalysis of any trial data that will test treatment effects…."[2]

However, to follow the logic and methods of the study, one would have to conclude that the answer to the analogous question of whether to offer thrombolysis to SPAN-100–negative patients (90% of all stroke victims and tested in 6350 such patients, 2445 having received thrombolysis in the selected database) would be no, most stroke patients should not be offered thrombolysis, as their study found no such benefit in that group (adjusted odds ratio, 0.96 [95% CI 0.85-1.07]).

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Conflict of Interest Disclosures: None reported.

1. Ovbiagele B, Reeves MJ, Nasiri M, Johnston SC, Bath PM, Saposnik G; VISTA-Acute Collaboration Steering Committee. A simple risk index and thrombolytic treatment response in acute ischemic stroke. *JAMA Neurol*. 2014; 71(7):848-854.

2. Ali M, Bath PM, Curram J, et al. The Virtual International Stroke Trials Archive. *Stroke*. 2007;38(6):1905-1910.

In Reply We thank Dr Little for his interest in our article.[1] Dr Little is correct in that "[t]he VISTA database does not sanction reanalysis of any trial data that will test treatment effects…." However, our observational study did not set out to reanalyze the efficacy of a given thrombolytic agent, but rather to assess the impact of thrombolytic agents administered as part of routine clinical practice in acute stroke trials of neuroprotective agents. We should also emphasize that our study should only be viewed as hypothesis generating. Indeed, the observation that older patients with more severe strokes gain more from intravenous thrombolysis treatment on an absolute scale simply leads to the conclusion that this group of patients may not necessarily have to be denied treatment just on the basis of age or stroke severity and that more study of intravenous thrombolysis use in elderly patients with severe strokes is needed. Finally, the lack of efficacy of intravenous thrombolysis in the SPAN-100–negative patients might have been because the nonrandomized assignment led to a residual treatment selection bias.

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1. Ovbiagele B, Reeves MJ, Nasiri M, Johnston SC, Bath PM, Saposnik G; VISTA-Acute Collaboration Steering Committee. A simple risk index and thrombolytic treatment response in acute ischemic stroke. *JAMA Neurol*. 2014; 71(7):848-854.

Treating Idiopathic Intracranial Hypertension

To the Editor In their article regarding the Idiopathic Intracranial Hypertension (IIH) Treatment Trial (IIHTT), Wall and colleagues stated that "there are no properly designed and executed clinical trials to guide therapy."[1] They quoted Lueck and McIlwaine[2] who correctly concluded a dearth of properly designed clinical trials in IIH at the time of their publication. In using this article, Wall et al[1] did not consider a number of important published studies in the intervening 5 years since this Cochrane review[2] was updated in 2008.

In 2011, Ball et al[3] prospectively evaluated acetazolamide use in mild IIH, similar to the IIHTT. Fifty patients were recruited and randomized to receive acetazolamide or no acetazolamide. Symptoms, body weight, visual function, and quality-of-life measures were recorded. Most showed improvement, with 44% judged to be in remission at trial end. Mean weight loss was 6.2 kg (5.8%) and 3.3 kg (3.5%) in the treatment arm and control arm, respectively. Difficulties with recruitment and poor compliance with acetazolamide were highlighted. Acetazolamide was discontinued in 48%.

Sinclair et al[4] reported a prospective cohort study in 2010 in patients with chronic IIH. Here, a low-energy diet for 3 months reduced intracranial pressure from baseline and was maintained 3 months after diet cessation. They also demonstrated improved symptoms and a reduction in papilledema, as objectively measured with optical coherence tomography and ultrasonography.

The major complication in IIH is severe and permanent visual loss, which fortunately is rare. The IIHTT considered that the rate of bilateral blindness in IIH is 10%. Best et al[5] published a British Ophthalmic Surveillance Unit study finding only 0.6% to 2% of new IIH cases would be expected to be severely sight impaired per year. Most patients with IIH have relatively mild visual loss; in many, there are issues in quantifying the visual deficit where disc swelling can mask the visual field and where there are nonorganic exaggerated visual field findings. In our experience, those who have severe visual loss present, or are not identified early enough, with fulminate disease.

The interest of this large IIH cohort really lies in whether the IIHTT can characterize the disease further than is currently known, in particular, whether the researchers are able to postulate disease mechanisms and what to consider targeting for treatment. We eagerly await the results of the IIHTT substudies investigating vitamin A metabolism and the genetic markers.

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1. Wall M, Kupersmith MJ, Kieburtz KD, et al; NORDIC Idiopathic Intracranial Hypertension Study Group. The Idiopathic Intracranial Hypertension Treatment Trial: clinical profile at baseline. *JAMA Neurol*. 2014;71(6):693-701.

2. Lueck C, McIlwaine G. Interventions for idiopathic intracranial hypertension. *Cochrane Database Syst Rev*. 2005;(3):CD003434.

3. Ball AK, Howman A, Wheatley K, et al. A randomised controlled trial of treatment for idiopathic intracranial hypertension. *J Neurol*. 2011;258(5):874-881.

4. Sinclair AJ, Burdon MA, Nightingale PG, et al. Low energy diet and intracranial pressure in women with idiopathic intracranial hypertension: prospective cohort study. *BMJ*. 2010;341:c2701.

5. Best J, Silvestri G, Burton B, Foot B, Acheson J. The incidence of blindness due to idiopathic intracranial hypertension in the UK. *Open Ophthalmol J*. 2013;28(7):26-29.

In Reply We thank Mollan and colleagues for their interest in our treatment trial.[1] We were aware of the pilot study by Ball and colleagues.[2] We stated that treatment of idiopathic intracranial hypertension is based on anecdotal and uncontrolled data because there were no properly designed and executed clinical trials to guide therapy prior to ours. We did not cite the Ball et al[2] pilot work because its results were inconclusive with respect to efficacy owing to the small sample size and consequent low power. Indeed, Ball et al stated in the article that "[t]his pilot study was not powered to detect a treatment effect."[2] Also, 12 of 25 patients in the acetazolamide group stopped taking the medication during the study, a discontinuation rate of nearly 50%. Dosing schedules for acetazolamide were at the discretion of the supervising clinician and did not reach more than 1500 mg per day. Twenty percent of the participants in the control group were eventually given acetazolamide. No conclusions could be drawn from their trial because of these study design issues.

We are also well aware of the study by Sinclair et al[3] that suggested that weight loss was associated with a decrease in cerebrospinal fluid pressure. While space limitations precluded us from discussing it in our article,[1] the results have a prominent place in the slide set we distributed to our investigators. The outcome of the Idiopathic Intracranial Hypertension Treatment Trial is now published.[4] Our diet-plus-acetazolamide group had twice the amount of weight loss as did the diet-plus-placebo group, and a mediation analysis showed that the effect of acetazolamide on improving vision was independent of its effect on weight loss.

We thank Mollan and colleagues for pointing out the Best et al study.[5] As Best et al[5] acknowledged, with studies like theirs, underreporting is a concern so the true incidence is not known. The figure of 10%, also cited in the Ball et al study,[2] comes from data from academic centers and is prone to selection bias. Best et al[5] reported a yearly incidence and we quoted a lifetime incidence. Needless to say, it is difficult to determine the true lifetime incidence of blindness in idiopathic intracranial hypertension.

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1. Wall M, Kupersmith MJ, Kieburtz KD, et al; NORDIC Idiopathic Intracranial Hypertension Study Group. The Idiopathic Intracranial Hypertension Treatment Trial: clinical profile at baseline. *JAMA Neurol*. 2014;71(6):693-701.

2. Ball AK, Howman A, Wheatley K, et al. A randomised controlled trial of treatment for idiopathic intracranial hypertension. *J Neurol*. 2011;258(5):874-881.

3. Sinclair AJ, Burdon MA, Nightingale PG, et al. Low energy diet and intracranial pressure in women with idiopathic intracranial hypertension: prospective cohort study. *BMJ*. 2010;341:c2701.

4. Wall M, McDermott MP, Kieburtz KD, et al; 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. *JAMA*. 2014;311(16):1641-1651.

5. Best J, Silvestri G, Burton B, Foot B, Acheson J. The incidence of blindness due to idiopathic intracranial hypertension in the UK. *Open Ophthalmol J*. 2013; 28(7):26-29.

CORRECTION

Incorrect Information in Tables and Figure Caption: In the Original Investigation titled "Genome-Wide Analysis of the Heritability of Amyotrophic Lateral Sclerosis," published in the September 2014 issue (2014;71[9]:1123-1133. doi:10.1001/jamaneurol.2014.1184), incorrect information appeared in Tables 2 and 4 and in the caption to Figure 1. On page 1125, the numbers 16 566 574, 16 505 937, and 17 070 203 in the last column of Table 2 should be replaced by the numbers 4 847 835, 4 835 273, and 4 894 283, respectively. In the first sentence of the caption to Figure 1 on page 1127, "study size" should be replaced by "effect size." On page 1128, the first part of Table 4 should read "Genotyped Data," and the second part should read "Imputed Data." This article was corrected online.