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EDITORIAL

High-Dose Glucocorticoids for Treating Sudden Hearing Loss: Cart before the Horse?

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Hearing impairment is the most common sensory deficit. It affects 2 to 3 of 1000 newborns and nearly 50% of adults 75 years of age and older in the United States.[1] Idiopathic sudden sensorineural hearing loss (ISSNHL) is characterized by an abrupt hearing loss requiring immediate diagnosis and treatment. Systemic glucocorticoids are widely used as the primary treatment for ISSNHL,[2] but no head-to-head comparisons of the effectiveness and risk profiles of high doses over a more commonly used lower dose of glucocorticoids have been conducted to inform standard-of-care practice.

In this edition of *NEJM Evidence*, Plontke et al.[3] report the results of a three-arm, randomized, triple-blind, multicenter trial that included participants (18 to 80 years of age) with sudden hearing loss of greater than or equal to 50 dB within 7 days of onset. Participants were randomly assigned to receive 5 days of high-dose intravenous prednisolone at 250 mg/day (HD-Pred), 5 days of high-dose oral dexamethasone at 40 mg/day (HD-Dex), or as a control, 5 days of oral prednisolone (Pred-Control) at 60 mg/day followed by 5 days of tapering doses. The primary end point was the change in hearing threshold in the three most affected contiguous frequencies from baseline to day 30. The trial was powered to detect a statistically significant improvement in each of the high-dose groups compared with the lower-dose control using two individual two-sample t-tests; the global alpha was 0.05 (two sided) when adjusted for two comparisons, each with a two-sided alpha of 0.025. With a final accrual of 101 to 105 participants per group, the sample size was indeed sufficient for also testing the third pairwise comparison between the two high-dose regimens (HD-Pred versus HD-Dex). The trial was terminated early because of the Covid-19 outbreak after completing 99% of its target accrual. The primary results of the trial showed no statistically significant difference between the three arms using a global analysis of variance test and precluded superiority of high-dose glucocorticoid therapy (HD-Pred or HD-Dex) over a lower-dose regimen (Pred-Control). Moreover, the high-dose arms were associated with an increased rate of side effects.

The authors are to be applauded for mounting this trial to compare the effectiveness and risk profiles of commonly utilized treatment strategies for ISSNHL, a cart-before-the-horse story; despite widespread acceptance of glucocorticoids as standard for primary treatment of ISSNHL, there are no data from prospective trials that compared the efficacy and safety of the regimens.[2,4] So, what could have been done differently? Are there other alternative design strategies in this setting that could have been utilized to better understand the dose–efficacy and dose–safety of the regimens? Possibly. The trial could have been

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designed to address the question in a multiphase approach by including a screening phase, in which multiple dosage levels and their interrelationships with covariates are investigated to identify the appropriate dose level, the appropriate target population, and any confounding factors, and a confirmation phase, in which the selected dose levels are evaluated in the identified target population, adjusting for the key covariates moderating the treatment effects. In such an approach, a type I error rate larger than the traditionally used P value of 0.05 can be selected in the screening phase because any selected doses from this phase will be further tested in a confirmatory trial. Another strategy is to rank different treatments by their standardized effect size and choose the one with the largest effect size rather than examining the statistical significance of each effect (i.e., the pick-the-winner design).[5,6] Such screening approaches require a smaller sample size than a traditional randomized superiority trial. When the selected dose levels are tested further in the confirmatory phase, the traditional type I error rate control should be used for formal hypothesis testing. Such a multiphase design strategy could have been utilized in this setting to investigate the dose (including, perhaps, no treatment), timing, and types of glucocorticoids: for example, with respect to the activation of mineralocorticoid receptors and glucocorticoid receptors for treatment of participants with ISSNHL during the screening phase. In addition, given that all three interventions are commonly given in practice, existing real-world data could have been used to design the trial differently: for example, noninferiority in efficacy outcomes between the lower versus higher dose of glucocorticoids for the treatment of ISSNHL versus testing for superiority.

In conclusion, the trial did not answer the question of whether there is a dose effect with glucocorticoids for treating ISSHNL. However, it provides valuable insights regarding the current treatment practice for sudden hearing loss, including demonstrating the increased risk of side effects associated with higher-dose glucocorticoids. It highlights the need for standardized reporting of hearing outcomes in clinical trials. Further research in this area is clearly warranted, including comparing glucocorticoid therapy with observation to understand spontaneous regression effects and studying the dose–efficacy and dose–safety of lower doses of the glucocorticoid therapy. The article also appropriately highlights the challenges with designing and executing clinical trials for inner ear drugs using regimens that are already in practice.

Disclosures

Author disclosures are available at evidence.nejm.org.

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