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Letter to the Editor

Letter to the Editor: "Intratympanic Administration of Edaravone for Sudden Sensorineural Hearing Loss: A Prospective Case Series with Historical Controls"

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Dear Editor,

The article by Nitta et al exploring the intratympanic administration of edaravone in the management of sudden sensorineural hearing loss (SSNHL) was read with great interest. The authors address an important and timely clinical question. While their efforts are commended, several observations that may help guide future investigations are respectfully offered.

The decision to use a historical control group without randomization raises the possibility of temporal and clinical confounding. While this approach is sometimes necessary, a randomized controlled trial (RCT) design would more effectively mitigate selection bias and support stronger causal inference. In addition, the small sample size (n = 17) and lack of an a priori sample size calculation limit the interpretability and generalizability of the findings.

Although the inclusion criteria conform to established Japanese Ministry of Health standards, the study does not stratify for key prognostic variables such as age, type and severity of hearing loss, or time elapsed since symptom onset. These factors have been well-documented to influence outcomes and should be considered in future study designs. Furthermore, the open-label nature of the investigation may introduce bias in the assessment of both subjective and objective outcomes.

To address these challenges, a double-blind RCT comparing two arms is proposed: (A) oral prednisone plus intratympanic corticosteroid (current standard of care) versus (B) oral prednisone plus intratympanic edaravone. The primary composite endpoint would consist of either complete audiometric recovery or subjective perception of normal hearing with only mild, symmetric residual loss. Secondary endpoints would include partial subjective improvement or an audiometric gain of ≥20 dB in at least three contiguous frequencies.

A sample size of approximately 193 participants per group would be required to detect a 10% absolute difference in recovery rates (65% vs 75%), assuming a two-sided alpha of 0.05, a power of 80%, and a design effect to account for minor clustering. This calculation also considers a 3% attrition rate and a precision target of ±10% in absolute risk estimates. These parameters and assumptions follow standard methodologies as outlined in authoritative references in biostatistics such as Fundamentals of Biostatistics.[1] The expected confidence interval for the absolute risk reduction would range from 2% to 18%, with a corresponding relative risk between 1.03 and 1.28, and a number needed to treat between 6 and 50.

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Given the potential for delayed auditory recovery, incorporating a time-to-event analysis using Kaplan–Meier estimates and Cox proportional hazards modeling would provide valuable information on the timing and durability of treatment effects.

The proposed design was developed in adherence to ethical considerations. Given that corticosteroids are widely accepted as standard therapy, withholding them in a control arm would be inappropriate. This proposal therefore evaluates edaravone as an adjunct while preserving standard treatment for all participants.

In summary, the current study provides preliminary data that may serve to stimulate academic interest in this therapeutic approach. However, due to numerous methodological limitations—including the lack of randomization, absence of sample size justification, and limited statistical power—these findings must be interpreted with caution. At this stage, they are insufficient to support definitive conclusions regarding efficacy or clinical applicability. Nevertheless, considering the positive trends observed and the existing evidence from randomized trials in neurological conditions such as amyotrophic lateral sclerosis[2] and stroke,[3] further investigation of edaravone in SSNHL through a methodologically rigorous, well-powered RCT appears both justifiable and timely.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Peer-review: Externally peer-reviewed.

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