Ethics of Placebo Control in Trials for Idiopathic Sudden Sensorineural Hearing Loss

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Given the current evidence, we propose that a placebo-controlled RCT of high-dose systemic steroids would be ethically acceptable.

Ethical Principles: Belmont Report, Declaration of Helsinki, and EMEA
The Belmont Report,6 the Declaration of Helsinki,7 and the EMEA (European Agency for the Evaluation of Medicinal Products)8 have established a set of ethical standards that should be applied to clinical research. They specifically assess how to deal with the use of placebo in a clinical trial (Figure 1).

Respect for persons is secured when (1) the autonomy of participants is established, (2) an appropriate informed consent process is carried out explaining the experimental nature of the trial as well as the risks and benefits, and (3) the participant makes a decision based on this information. These points should be included in any new trial as part of the shared decision process with the patient. As for beneficence, the use of placebo in a trial requires considering the risk-benefit balance such that research subjects should not be banned from getting the best treatment available. In our case, there is lack of evidence to support systemic corticosteroids for ISSHL.4 The Spanish ENT Society’s guidelines9 recommend corticosteroids based on incomplete data (ie, trials of small size and with risk of bias). The 2011 version of the German guidelines recommends corticosteroids.10

When a systematic review of all the existing data was performed,4 the conclusion was that the value of corticosteroids for ISSHL remains unclear and that the 3 existing trials (Cinamon,11 Nosrati-Zarenoe,12 and Wilson13) had too many confounders to draw any decisive conclusion (ie, the populations were too small, and the dosage, formulation,
and duration of steroid treatment varied). These trials are summarized in Table 1.

Solidly established clinical practices can be challenged and modified by systematic reviews. Consider an example that not only created a situation of equipoise but eventually modified a practice through a new conclusive clinical trial regarding the use of systemic corticosteroids for traumatic brain injury. Corticosteroids have been widely used in brain trauma because they were thought to reduce intracranial pressure. However, after corticosteroid use, the brain may swell, thereby causing raised intracranial pressure—a potentially fatal condition. An inconclusive Cochrane review was carried out in 2000, but a subsequent large randomized placebo-controlled trial showed a significant increase in number of deaths among patients given corticosteroids, suggesting that they should no longer be routinely used in patients with traumatic head injury.

We can analyze the principle of justice with consideration of individual participants and society as a whole. Subjects who participate in a placebo-controlled trial may receive a benefit from systemic corticosteroids, if such benefit really exists; however, those receiving placebo would not be exposed to the unwanted effects of corticosteroids. If

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**Figure 1.** Ethical criteria for the use of placebo from the Belmont Report, the Declaration of Helsinki, and the EMEA (European Agency for the Evaluation of Medicinal Products).

**Belmont Report:**
1. Respect for persons. Individuals should be treated as autonomous agents, and persons with diminished autonomy are entitled to protection.
2. Beneficence. Treating persons in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being.
3. Justice. This refers to the distribution of the benefits and burdens of research.

**Declaration of Helsinki:**
1. No proven intervention exists, the use of placebo, or no intervention, is acceptable; or
2. For compelling and scientifically sound methodological reasons and,
3. The patients will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

**EMEA:**

A placebo control would be acceptable if:

1. The period of use of the placebo does not entail any additional risk of irreversible harm to the patient.
2. The participant or his/her legal representative receives and understands appropriate information on the trial, and give informed written consent.
3. The participant has the right to withdraw at any time, and still receive conventional treatment.

The EMEA states that forbidding placebo-controlled trials in therapeutic areas where there are proven treatments would preclude obtaining reliable scientific evidence for the evaluation of new medicinal products, and be contrary to public health interest.
Table 1. Risk-of-Bias Analysis in the Trials Included in Wei (2013). 4

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<tr>
<td>Patients, n</td>
<td>41</td>
<td>103</td>
<td>123</td>
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<tr>
<td>Intervention</td>
<td>Prednisolone tablets (1 mg/kg/d); duration, 5 d</td>
<td>60 mg, prednisolone, single daily dose (10-mg tablets); duration, 3 d. After these 3 d, daily reduction of 10 mg/d, with a total duration of 8 d.</td>
<td>Different in the 2 hospitals involved in the study: (1) tapering oral dexamethasone dose over 10 d and (2) oral methylprednisolone with a different tapering dose over 12 d. The authors did not clarify the nature of the placebo and its dosage schedule.</td>
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<td>Control arm</td>
<td>Placebo tablets</td>
<td>Placebo</td>
<td>Placebo (not clarified its nature) Randomized controlled trial</td>
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<td>Study type</td>
<td>Randomized controlled trial</td>
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<td>Conclusions</td>
<td>There was no statistical difference in the hearing improvement rates at 6 frequencies (from 250 to 8000), average speech frequencies (5000, 1000, and 2000), and high tone average (4000 and 8000).</td>
<td>No significant difference in hearing recovery between the prednisolone and placebo groups either at day 8 or 3 months (P &gt; .05).</td>
<td>The total percentage of patients with hearing improvement was 61% in the steroid group and 32% in the placebo group (relative risk, 1.30; 95% confidence interval, 0.91-1.86). However, this is the combination of results from 2 centers with a different steroid dosage and with different demographic patient groups. The authors simply added up numbers of participants across the 2 centers.</td>
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<td>Limitations</td>
<td>Randomization into 4 treatment groups achieved by rotation (first patient allocated to group 1, second to group 2, etc). Because the sample was too small, the randomization method was not adequate. Due to the low recruitment levels, there was an uneven distribution (by chance) of patients with known and conceivably unknown factors that could affect the outcome. For instance, the corticosteroid study group had fewer patients with vertigo and tinnitus.</td>
<td>The authors mentioned that neither the person who administered the treatment nor the person evaluating the response to treatment knew which treatment a particular participant was receiving. However, they did not clarify the method of randomized allocation of participants to each treatment group. The randomization appeared to be adequate, as there was an even distribution of sex, age, audiogram types, onset and severity of hearing loss, and associated symptoms of tinnitus and vertigo. The intention-to-treat analysis was not achieved, as 30 patients were excluded from the analysis after they were assigned to the study groups.</td>
<td>The quality of randomization of patients into the different study groups was poorly defined in the study. Randomization was inadequate, and this resulted in a selection bias. This conclusion is supported by the uneven distribution of the age, symptom of vertigo, audiogram types, and number of the participants between the different treatment groups and between the 2 centers in which the trial was carried out. The authors also erroneously assumed that the untreated control group and the placebo group were similar enough to be combined as one single control group, which significantly increased the control group population compared with the small number of participants in the corticosteroid treatment group. This annulled the effects of randomization and brought confounders into the analysis.</td>
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corticosteroids are indeed effective for ISSHL, then all patients with the condition would indirectly benefit from the study’s confirmation of their effect. The benefit for society would be significant because, if corticosteroids were not effective, we would avoid exposing patients to a treatment that is not free from harmful effects.

**Declaration of Helsinki**

*First principle: Placebo is acceptable if no proven intervention exists.* The latest and most compelling evidence does not support the use of corticosteroids for ISSHL. Even when systemic corticosteroids appear to be the standard of care, there is an effective situation of equipoise, as in the example of corticosteroids for brain injury explained above.

*Second principle: Placebo is acceptable for compelling and scientifically sound methodological reasons.* It has been stated that it is more correct to compare a new drug against placebo through a superiority trial than against another treatment through an inferiority design. Specifically, if the new drug is found to be as good as the conventional treatment, it could be that neither of them are more effective than placebo.

*Third principle: Equipoise.* The third principle is pertinent here precisely because of the reason for a new placebo-controlled trial: the lack of a “best proven intervention.”

**EMEA**

Because there is equipoise, using placebo does not entail an indisputable risk or an irreversible harm to the patient (the first principle). This trial should be designed to secure the second principle: the patient’s understanding the appropriate information and giving informed written consent. Besides, the participant will have the right to withdraw at any time and still receive conventional treatment (the third principle).

Additional proposed features of a placebo-controlled trial for ISSHL include the following.

**Safety monitoring and interim analyses.** A careful data safety monitoring plan and a series of interim analyses will detect imbalances on the efficacy or safety of the treatments at an early stage, which would allow for an early termination of the study, if required. From an ethical standpoint, this tool would improve the benefit-risk ratio of the trial. There should not be significant differences between allocation groups in the distribution of severity of loss, audiogram shape, presence of vertigo, and age, which seem to affect the prognosis of ISSHL and could therefore be confounders.

**Randomization.** Proper randomization would aim to control for both known and unknown confounders.

**Weekly audiometry tests.** At least weekly audiometry tests should be conducted. Because most recovery occurs within the first 2 weeks after onset, a reasonable termination end point would include significant recovery differences in the interim analysis of the first week, considered as a loss of at least 30 dB in 3 connected frequencies—that is, what the

National Institute of Deafness and Other Communication Disorders uses as a threshold to define ISSHL. Moon et al found that the beginning of hearing improvement took place within the first 2 weeks after treatment initiation in 93.1% of patients and that a complete recovery or an end of change was cumulatively achieved in 80.4% of the patients within 1 month and in 92.2% of the patients within 2 months after treatment. Based on this, the Spanish ENT Society’s guidelines recommend a control audiometry at 1 week after treatment. Based on the results of Yeo et al, the American Academy of Otolaryngology—Head and Neck Surgery Foundation’s guidelines support follow-up audiometry within 3 to 6 months of initiation of treatment according to expert opinion and acknowledge that slightly shorter or longer periods of follow-up would not be unreasonable. Because we intend to be able to detect differences between groups as soon as possible, we propose the shortest of the periods described as the time to do the interim audiometric analysis: 1 week.

**Rescue treatment.** Because we start from an equipoise situation, it could be argued that a “rescue” treatment with corticosteroids would not be necessary for nonimproving participants. However, we understand that if a patient who was allocated to placebo did not recover at all (or continued to worsen), a salvage switch to the corticosteroid treatment would also be a defensible option.

**Quality of life.** Quality of life should be included as a main outcome of the trial, given its practical importance for the patient. The Medical Outcome Short Form–36 Health Survey, the Short Form Health Survey Version 2, the EuroQoL 5D, the Problems Impact Rating Scale, the Hospital Anxiety and Depression scale, and the Hearing Handicap Inventory have been used to measure quality of life among ISSHL patients.

**Conclusions**

Ethical concerns may arise from the use of placebo in a trial for ISSHL. Given the current evidence, there is equipoise that justifies such a trial. It will need a robust data safety monitoring plan and an interim analysis to detect imbalances on the efficacy and safety of the trials at an early stage and to stop the trial if needed.

**Author Contributions**

Miguel Maldonado Fernández, designing and writing the manuscript; final draft version; Susan Kornetsky, significant contributions through discussion; review of the manuscript; expertise contribution; Laura Rubio Rodriguez, significant contributions through discussion; review of the manuscript.

**Disclosures**

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