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Efficacy and safety of corticosteroids and magnesium supplement in sudden sensorineural hearing loss: a protocol for a double–blind, randomized controlled trial

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STUDY PROTOCOL

Efficacy and safety of corticosteroids and magnesium supplement in sudden sensorineural hearing loss:

a protocol for a double–blind, randomized controlled trial

Korda Athanasia, Department of Otorhinolaryngology, Larisa General University Hospital, Greece

Abstract

Introduction: Hearing loss affects communication, compromising quality of life, and is therefore associated with social costs as well as the economic costs of medical treatment or hearing aids (3). Magnesium treatment has been repeatedly shown to reduce the incidence of both temporary and permanent noise-induced hearing loss and also the protective effects of magnesium on hearing loss is well established in animal studies but in few human studies(3).

Purpose: We hypothesized that it might also improve the permanent threshold shift in patients with acute-onset hearing loss. So we want to investigate the benefit of magnesium supplement combined with standard treatment of sudden sensorineural hearing loss (SSNHL) patients.

Methods: This study proposes a randomized, double- blind, placebo-controlled parallel trial to assess the efficacy and safety of a combination of corticosteroids and magnesium (400mg daily) in sudden hearing loss. Audiological testing comprising of pure tone audiometry and speech-in-noise testing will be performed.

Results: By use of a mixed effects statistical model, the effects of magnesium compared to placebo intake will be assessed.

Conclusion: Magnesium is a relatively safe and convenient adjunct to steroid treatment for enhancing the improvement in hearing, especially in the low-tone range, in patients with sudden sensorineural hearing loss.

INTRODUCTION

Sudden sensorineural hearing loss (SSHL) is the term used to describe the abrupt onset of hearing loss of at least 30 dB in three consecutive frequencies on a standard audiogram (1). Incidence of SSNHL ranges from 5 to 20 patients per 100,000 per year; the mean overall age of affected patients is between 46 and 49 years, with the lowest incidence in the 20–30 year age group and the highest in the 50–60 year age group. In general the incidence seems to be equally distributed between the sexes. It is generally a unilateral process (approximately 98%), and functional hearing recovery without treatment was observed in up to 65 percent of patients (12, 15).

Although many theories have been proposed, the ultimate etiology remains unknown. Among the many proposed causes of this condition are viral infection and the resultant inflammation, breaks in Reissner's membrane causing persistent depolarization of hair cells due to the disruption of the appropriate ion gradient(2), and vascular insult to the cochlea(4). Given that this condition is currently defined by clinical criteria, it may be that each of these mechanisms is responsible for a proportion of the total number of observed cases.

The discovery that the formation of free radicals in the inner ear is a key factor in hearing loss (5–10) suggests that antioxidants may play a preventive or therapeutic role. Recently, several animal studies have suggested that antioxidants act synergistically with magnesium intake to prevent hearing loss (7, 10). Magnesium is known to reduce noise-induced vasoconstriction that occurs as a result of free radical formation (7,24–25). Few epidemiologic studies have shown a protective effect of magnesium intake on hearing loss (20, 25), and we know of no epidemiologic studies that have examined the potential joint effects of corticosteroids and magnesium. The most widely accepted therapy is the use of steroids, administered systemically or intratympanically, alone or in combination.

The disadvantages of systemic treatment with steroids are well-known long-term complications. (16-19)

The present article proposes a protocol for a clinical study consisting of a double-blind, randomized, placebo-controlled trial with a combination of standard corticosteroid therapy and Mg++ supplement in humans after sudden hearing loss.

The present report will follow the guidelines expressed by Consolidated Standards of Reporting Trials (CONSORT)

SUBJECTS AND METHODS

Design

This study proposes a randomized, double-blind, placebo-controlled parallel trial. Participants need to experience a sudden hearing loss which must be proved by an audiologic test. The loss of hearing must be at least 30 db at three consecutive frequencies. The symptoms of hearing

loss must have recent onset-24h.Each participant need to take the treatment (corticosteroids and Mg or placebo) for a month and an audiogram will be done almost weekly during the treatment protocols in both the groups. One at the start, one after the 5 days therapy with prednisone, one at the meantime and the last at the end of the whole therapy with magnesium. This study aims to investigate the combined effects of Corticosteroids and Mg2+ in sudden sensorineural hearing loss in adults.

Recruitment

We will recruit adults with sudden sensorineural hearing loss from August 2015 until July 2017 that will be admitted to the ENT clinic department of Larissa University Hospital. In order to recruit a fair number of patients we will send e-mails to all the private ENT doctors of Thessaly that often come across with this entity, and we will endorse them to admit the patients to the hospital. In addition, at the stage of enrolment it will be determined which occasions the subjects will attend and test moments will be scheduled. The aim is to plan all treatments within the range of one month in order to reduce the risk of drop-out

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Treatment protocol

After screening for eligibility, patients consenting to enroll will be divided randomly in two groups. Both groups will be similar regarding age, gender, season of the year in which deafness occurred, presence of vestibular symptoms and tinnitus, therapeutic delay from initial symptoms to start of treatment, and initial hearing loss. A group will receive a combination of corticosteroids and Mg++ and B group corticosteroids and a placebo drug. Each participant will receive the same dose of corticosteroids as standard treatment which is prednisone 1 mg/kg/d x 5 d and a packet with a pill of 200mg Mg or placebo twice a day. The participants will receive the 5 days therapy at the ENT clinic and they will continue at home by receiving only magnesium or placebo for one month.

In 50%, the packets contain a placebo pill with an identical appearance and weigh as Magnesium (similar color-taste). All participants (as well as the researchers) will be blinded to the order of magnesium and placebo.

Safety assessment

Adverse events are defined as symptoms occurring after the administration of magnesium and corticosteroids or placebo that are not necessarily related to the intervention. Participants will receive telephone number to report adverse events during the study and will be urged to come to the clinic in case of serious adverse events.

The criterion adopted in this study to assess a therapeutic effect was an average improvement of 10 dB on Audiograms. This criterion was the widest adopted in the recent analysis on argument published in English literature (16-19).

Adherence assessment

After discharged from the hospital the participants will be given 60 pills each in 60 closed envelopes. These envelopes will be requested at the end of the therapy in order to ensure that the participants take all the pills.

Permitted and prohibited concomitant treatments

The use of alcohol and tobacco is limited to a maximum of two alcohol consumptions and to two cigarettes daily. Other psychoactive drugs are strictly prohibited

The study will be approved by the local Research Ethics Committee and it will be performed in accordance with the ethical standards laid down in the 2000 Declaration of Helsinki as well as the Declaration of Istanbul 2008.

Follow-up

The patients will be followed-up for one month. Patients lost during the follow-up and with evidence of retrocochlear disease at MRI (i.e., vestibular schwannoma) will be excluded from the analysis.

Inclusion criteria

The inclusion criteria are as follows:

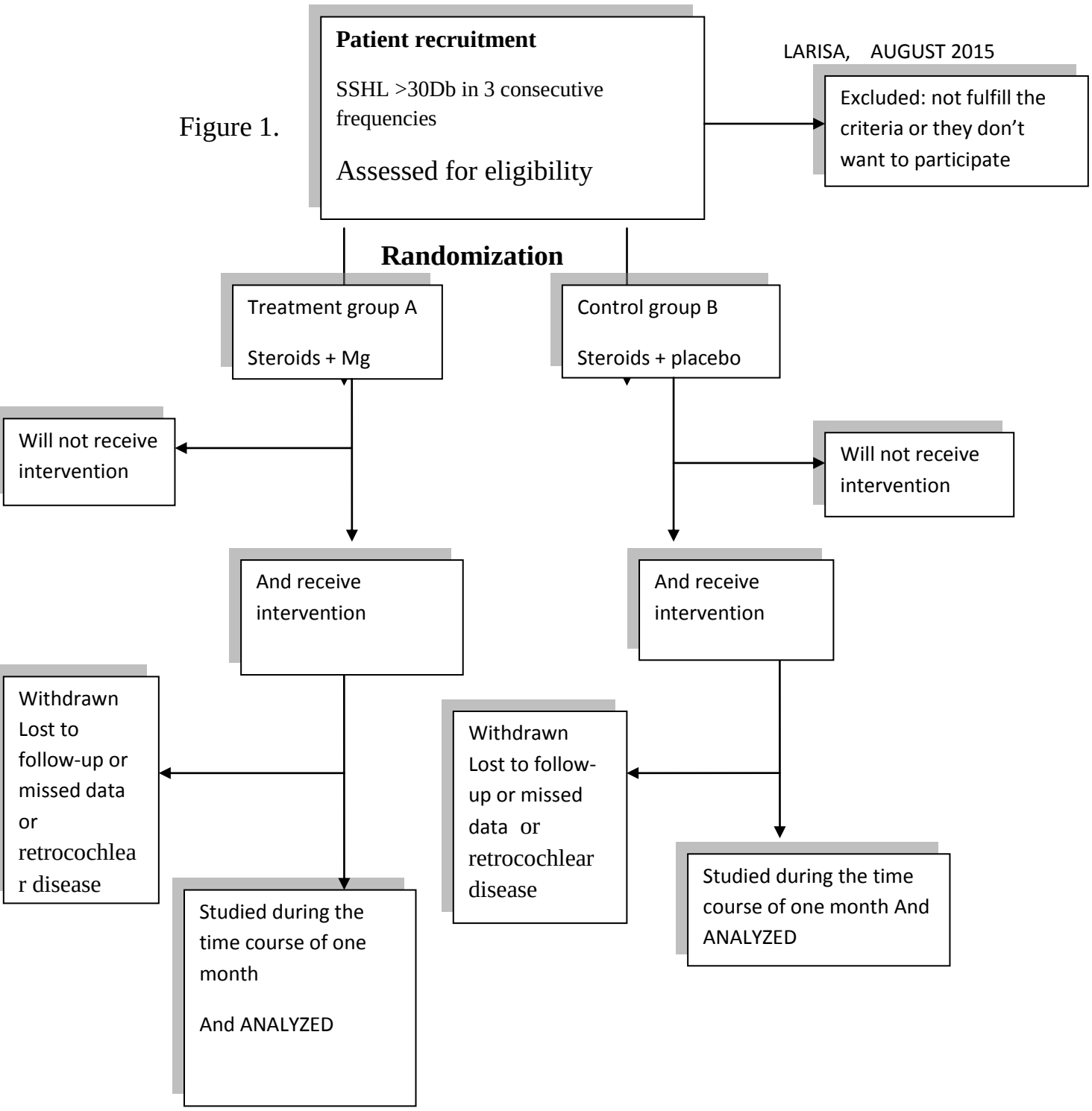
- Hearing loss 30db at 3 consecutive frequencies
- Willingness to take treatment
- Age between 18 and 60 (males as well as females)
- Recent onset of hearing loss ≤ 24h
- No prior treatment

Exclusion criteria

The exclusion criteria are as follows:

- Middle ear pathologies such as otitis media and the perforation of the tympanic membrane and history of such pathologies.
- Previous episode of hearing loss
- Known allergies for corticosteroids or Mg++
- Diabetes
- Pregnancy

Figure 1.



Patient evaluation

Thorough history, otoscopy, bedside peripheral vestibular system examination, pure tone audiometry(repeated weekly), and MRI of internal auditory canal and cerebello-pontine angle. History detailed: onset of hearing loss, ontological symptoms related with hearing loss, drugs consumed in the past few days, and presence of others systemic diseases. The bedside examination was done by spontaneous and positional nystagmus, Romberg test, Unterberger test, Halmagyi test, and Head shaking test.

Randomization

The production of the corticosteroids with magnesium and placebo packets as well as the randomization of the ABAB protocol will be performed by an independent pharmacist. The packets of medicines and placebos will be labeled with a number corresponding with the numbers on the forms. The randomization file will be put into a sealed envelope and retained in a safe at the pharmacy. The randomization table will not be available for assessment by anyone else involved in the study. At the end of the study the envelope will be requested.

Sample size calculation and statistical analysis

A power approach calculation was performed in order to make an estimation of the sample size needed to detect significant differences in the audiograms between the experimental and control group. A two-independent groups test in which an α-level of 0.05 and a nominal power of 90% will be used. A 10-dB average difference in hearing outcome between treatments will be defined as clinical important.
Standard deviation for the comparison is known to be equal to15db between the pre- and post-therapy measurements on the audiogram (taken into consideration the literature), a calculation showed a requirement of at least 48 participants. Because of the potential loss we add 10% more. So we need at least 53 participants. We will recruit 54 patients 27 in each arm.
All data in this trial will be assessed with SPSS Statistics version 21.0. Because multiple correlated measurements will be performed in the same participants, a mixed effects model will be applied. This analysis is preferable over more traditional approaches such as repeated measures analysis of variance (ANOVA) because of the advantages to deal with missing values.

RESULTS

Outcomes
The primary outcome measure will be the evaluation of a significant average difference in test results of the Audiological testing (audiometry and speech-in-noise tests) when comparing the placebo results to the medicine trials.

Main outcome measures

Pure tone audiometry Pure tone liminiar audiometry will be performed according to the current clinical standards using a two-channel AC40 Audiometer in a silent room. Air conduction thresholds will be measured under headphones at 125 Hz, 250 Hz, 500 Hz, 1 kHz, 2 kHz, 4 kHz and 8 kHz. When air conduction

thresholds between 250 Hz and 4 kHz exceed normality levels of 20 dB HL, the bone conduction threshold will be measured on ,250 Hz, 500 Hz, 1kHz, 2kHz and 4kHz in order to make a distinction between conductive and sensorineural hearing loss.

Secondary outcome measures

Speech discrimination testing Speech discrimination, as opposed to speech sensitivity, is the person's ability to not only hear words but to *identify* them. The procedure includes presentation of 50 selected monosyllabic words at an easily detectable intensity level. The speech discrimination score (SDS) is the percentage of words correctly identified. Pathology of the inner ear, auditory nerve, and/or central auditory pathways can affect this score. The ability of an individual to discriminate speech is not well predicted by the pure-tone audiogram. An individual may hear a sound well enough, but the neural signals may be altered to the extent that the sound is unintelligible.

Individuals suffering only a conductive hearing loss will be able to identify words if the sound is loud enough. For persons with sensorineural hearing loss, there is a marked drop in the score without a proportionate loss of pure-tone or speech sensitivity.

Data and safety monitoring

Monitoring will be conducted for quality control. Investigators will also be convened to discuss practical issues that might be encountered, such as dealing with serious adverse events, revising the protocol, and addressing certain important issues that might be raised by investigators and participants. We define adverse events as unintended signs, symptoms, or disease occurring after treatment that were not necessarily related to the intervention. The safety assessment will be based primarily on the frequency of adverse events, which included all serious adverse events. Information regarding adverse events was summarized by presenting the number and percentage of participants experiencing any adverse events.

Ethics

All procedures that will be followed will be in accordance with the ethical standards of the responsible committee on human experimentation (institution and national) and with Helsinki Declaration of 1975, as revised in 2000.Written consent will be obtained from each participant.

Dissemination policy

According to the Standard Protocol Items: Recommendations for Interventional Trials(SPIRIT) guidelines, the authors declare that data that break the blind will not be presented prior to the release of mainline results. The breaking of the blind will occur at the end of the study. A clinical article will be written on the primary (including also secondary) outcomes of the study and results will be disseminated regardless of the magnitude or direction of effect. The present trial is not industry-initiated. As such, there are no publication restrictions imposed by sponsors. In addition, a full study report, anonymized participant- level dataset and statistical code for generating the results will be made publicly available no later than 3 years after the termination of the study for sharing purposes.

CONCLUSION

Several medical treatment regimens are available to treat SSNHL, either in combination or alone. There is no universally accepted treatment for SSNHL. In fact, treatment itself is controversial since the rate of spontaneous recovery for SSNHL is often comparable to that reported for treated patients. Mattox and Simmons reported that the spontaneous recovery rate in SSNHL was 65% (12). Recently, Cinamon et al. conducted a prospective double-blind placebo-controlled study including steroid, carbogen and placebo (23). Results revealed no significant difference between the treatment and placebo groups.

The authors acknowledge the limitation of not including blood samples in the present protocol in order to control for naturally varying Mg++ levels in the individual. However, the investigators considered that it was very likely that the drop-out would be very high when participants needed to give a blood sample at every test moment.

To our knowledge, this study is the first to combine steroids and Mg2+ as therapy for sudden hearing loss in adults performed in a randomized, placebo controlled trial. Furthermore, both participants and investigators will be blinded for the sequence of Mg and placebo. Thus, this would not influence on one hand the participants and on the other hand the investigators in performing the Audiological testing, limiting investigator bias as far as possible.

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