The effects of magnesium supplementation on sensorineural hearing damage: A critical review of the literature

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This critical review examines the effects of magnesium supplementation on auditory damage associated with noise-induced and idiopathic sudden sensorineural hearing loss. Study designs included three randomized, placebo-controlled trial experiments and one crossover experiment. Overall, evidence suggests that there is potential for magnesium supplementation as a treatment for noise-induced and idiopathic sudden sensorineural hearing loss in adults. It is recommended that additional studies be completed with larger and more diverse subject populations and with proper controls to account for the effects of presbycusis, noise-exposure, auditory disease, and individual magnesium levels. It is also recommended that additional studies be completed to determine proper dose response curves and best means of magnesium administration.

Introduction

Hearing loss affects millions of people worldwide and has the potential to negatively impact communication, relationships, and quality of life (World Health Organization, 2009). The National Institute on Deafness and Other Communication Disorders (NIDCD) (2009) defines sensorineural hearing loss as hearing loss caused by damage to the sensory cells of the inner ear, and/or the vestibulocochlear nerve. This type of hearing loss may be present at birth or appear later in life; it can be stable, progressive or fluctuating, and is potentially permanent. Sensorineural hearing loss can be caused by a number of known factors including genetics, noise, and disease (NIDCD, 2009). In some cases the cause is unknown and is termed idiopathic or sudden sensorineural hearing loss (NIDCD, 2009). Presently, prevention and hearing prostheses are the only sensorineural hearing loss "treatments" available. However, hearing protection may be impractical or inadequate and there are instances where amplification has proved unsuccessful in the treatment of hearing loss. Furthermore, success with these prevention and treatment strategies relies on cooperation, motivation, and overall compliance with prevention and prosthetic recommendations. For these reasons new treatments are undeniably necessary.

Studies completed with animal models suggest that magnesium supplementation can reduce the amount of hearing damage associated with noise exposure (Ising, Handrock, Guenther, Fischer, Dombrowski, 1982; Scheibe, Haupt, Vlastos, 2000; Joachims, Babisch, Gunther, Handrock, 1983). Joachims et al. (1983) found that rats with a magnesium infused diet experienced less hearing loss when exposed to impulse noise. In a preliminary attempt to apply this knowledge using a human model, investigators looked for a correlation between hearing loss severity following noise exposure and magnesium serum levels (Joachims, Ising, Gunther, 1987). It was found that humans with higher magnesium serum levels experienced less severe hearing loss following noise exposure (Joachims, Ising, Gunther, 1987).

In general, definitive research on this subject is difficult because many factors including heredity, age, and exposure, contribute to hearing loss. Nonetheless, research in this area is a crucial precursor to clinical trials, which may revolutionize the way in which sensorineural hearing loss is treated.

Objective

The primary objective of this review is to outline and critically evaluate all available studies that have examined the effects of magnesium supplementation on sensorineural hearing damage in adults.

Methods

Search Strategy

Computerized databases including CINAHL, CommDisDOME, Medline, PubMed, and SCOPUS were searched using the following keyword search strategy: (Magnesium or Mg) and (Hearing or Auditory or Cochlea or Sensorineural) or (Noise or NIHL or Idiopathic). The search was limited to journal articles and reviews published in English before November 2009 that used human research subjects.

Selection Criteria

Studies included in this review examined the effects of magnesium supplementation on sensorineural hearing damage in adult subjects. Two studies examined the effects of magnesium on subjects with idiopathic sudden sensorineural hearing loss, one examined the effects of magnesium supplementation on noise-induced permanent threshold shift, and one examined the effects of magnesium on noise-induced temporary threshold shift. No limits were placed on subject demographics or type of outcome measure; however, all studies minimally obtained pure tone thresholds. Accepted studies were all conducted in Israel.

Data Collection

The literature search yielded four articles consistent with the selection criteria. The intention was to collect all peer-reviewed articles that focused on the effects of magnesium supplementation on sensorineural hearing damage in adults.

Results

Study #1. Nageris, Ulanoviski, Attias, and Tikva (2004) used a prospective, randomized, double-blind placebo-controlled trial to investigate the effectiveness of oral magnesium supplementation in the treatment of sudden sensorineural hearing loss (SSHL). Subjects diagnosed with idiopathic SSHL (n=28) were randomly assigned to either the control group, which received steroid treatment plus a placebo, or to the treatment group, which received steroid treatment plus magnesium supplementation. All subjects began treatment within 48 hrs and audiometric testing was completed before and after treatment. Statistical significance was determined using repeated measures and unpaired t-tests. Group data analysis showed that the treatment group had a greater proportion of subjects with improved hearing thresholds at all test frequencies ($F=4.8$, $p<0.02$) and an overall greater mean improvement ($F=3.7$, $P<0.05$). Overall, these results suggest that magnesium supplementation can enhance steroid treatment of SSHL.

Study #2. Gordin, Goldenberg, Golz, Netzer, & Joachims (2002) completed a prospective, randomized, placebo-controlled trial to investigate the effectiveness of magnesium treatment for improving the outcome of unilateral idiopathic sudden hearing loss (ISHL). Subjects were all recruited from the same institution and blinding was not possible due to the nature in which the magnesium was administered. Subjects diagnosed with ISHL (n=278) were randomly assigned to either the control group, treated with carbogen inhalation or to the treatment group, treated with intravenous magnesium and carbogen inhalation. Subjects were later excluded from the control group for additional treatment (n=20) and from the treatment group due to side effects associated with magnesium (n=10). In addition, several subjects were also lost from the control (n=59) and the treatment group (n=56) during follow-up procedures. Subjects began treatment at various times, but within a two-week period. Treatment continued until hearing was determined to be normal or similar to the better hearing ear. Standard audiometric testing was completed every second day during hospitalization as well as one week and one month after discharge. Improvement rate was calculated using the following formula.

$$\text{Improvement rate (\%)} = \left(\frac{\text{Initial PTA-Final PTA}}{\text{Initial PTA - PTA of the opposite ear}} \right) 100$$

This formula, first described by Shiraishi, Kubo, Okumura, Naramura, Nishimur, Okusa, and Matsunaga (1993), recommends without justification that subjects with pure tone averages in the unaffected ear of 40dB or more be excluded from improvement rate analysis. For the purpose of their study, Gordin et al. (2002) defined recovery as an improvement rate greater than 75%. An improvement rate of 46% to 75% was interpreted as good, an improvement rate of 20 to 45% as fair, and an improvement rate less than 20% as no improvement. PTA was calculated using the mean of six bone conduction frequencies (250-8000Hz) and statistical significance was determined using Chi Square and Student's t-test. Recovery was achieved in 48% of the treatment group and 31.6% of the control group ($p<0.01$) and the mean improvement rate was reported as 66.4% in the treatment group and 49.9% in the control group ($p<0.01$). Good improvement was seen in 27.4% of the treatment group and 23.3% of the control group and fair improvement was seen in 10.9% of the treatment group and 20% of the control group. No improvement was seen in 13.6% of the treatment group and 25% of the control group. Overall, these results suggest that magnesium treatment may improve recovery in cases of ISHL.

Study #3. Attias, Weisz, Almog, Shahar, Wiener, Joachims, Netzer, Ising, Rebentisch, & Guenther, (1994) conducted a prospective, randomized, double-blind, placebo-controlled trial to investigate the prophylactic value of long-term oral intake of magnesium in reducing noise-induced permanent threshold shift. Male subjects (n=300) had audiometric evaluations prior to beginning a 2-month military training camp. Subjects were randomly assigned to either the control group, which received a daily placebo drink or to the treatment group, which received a daily magnesium supplement drink. All subjects experienced a similar lifestyle in terms of noise exposure, diet, and

daily routine. Statistical significance was determined using repeated-measures multivariate analysis of variance, paired and unpaired Student's t-tests, Chi-square and Mantel-Haenszel Chi-square tests, and Pearson correlation. Results revealed that the placebo group had significantly more frequent and severe permanent threshold shifts (x^2=8.1, p<0.001). Overall, these results suggest magnesium supplementation may reduce noise-induced permanent hearing damage.

Study #4. Attias, Sapir, Bresloff, Reshef-Haran & Ising (2004) evaluated the effects of magnesium intake on temporary threshold shift. A prospective, double-blind crossover design was used. Normal-hearing male subjects (n=20) participated in three measurement sessions: (1) a baseline measurement prior to any treatment, (2) a measurement 10 days after daily oral magnesium treatment, (3) a measurement 10 days after daily placebo treatment. The second and third sessions were double-blind and after the initial baseline session the last two sessions were randomly assigned. Subjects were exposed to 90 dB SPL white noise for a 10minute duration and audiometric evaluations were conducted prior to and after noise exposure until thresholds returned to normal. Statistical significance was determined using Wilcoxon paired sign rank tests and McNemar nonparametric univariate tests. Due to the repeated test measure design, only two probabilities of less than 0.015 were considered significant. Results revealed that magnesium treatment was associated with significantly lower temporary threshold shift (Baseline measurement: 2kHz df=1, x^2=8.067, p<0.005; 3kHz: df=1, x^2=6.4, p<0.011; Placebo measurement: Placebo group:3kHz df=1, x^2=4500, p<0.034; 4kHz: df=1, x^2=4500, p<0.034; 8kHz: df=1, x^2=0.444, p<0.02). The results of this study suggest that magnesium supplementation can reduce noise-induced temporary threshold shift.

Discussion

Magnesium is involved in the regulation of cell membrane permeability, neuromuscular excitation, and energy consumption and production (Guenther, Ising, Joachimsm 1989). Within the inner ear, it alters the permeability of the sensory hair cell membranes, such that a deficiency results in an increase of intracellular calcium and sodium and a decrease in potassium by passive diffusion (Attias et al., 1994). This diminishes the electrochemical gradient required for sensory transduction. In an attempt to restore this gradient, the hair cells expend energy, which can ultimately lead to cell death (Attias et al., 1994). It is also thought that extracellular magnesium deficiency leads to the release of hormones that decrease muscle tone, thereby reducing blood flow to the cochlea (Thorne & Nuttall, 1987); this too depletes cell energy and can be associated with cell death. Metabolic stress within the inner ear, such as that caused by noise exposure, places high demands on cell energy stores (Spoendlin, 1962). If magnesium is deficient in addition to the demands caused by noise exposure, the potential for hair cell damage is greater (Attias et al., 2004).

The exact mechanism by which magnesium supplementation works remains unclear. However, it is speculated that supplementation increases magnesium levels within the inner ear to maintain normal membrane characteristics and cell energy demands. Increased magnesium levels are also thought to improve the microcirculation of the inner ear, therefore, improving blood flow to the cochlea (Altura, Altura, Gebrewold, Ising, Gunther, 1992). This review examined four studies that investigated magnesium supplementation as a potential treatment for hearing damage in humans. The results provided by these four studies should be interpreted with caution, as a number of procedural shortcomings exist.

Sample size, subject withdrawal, and subject pool selection are the first matters of contention affecting result validity. Half of the studies had a small sample size of 20 and 28 subjects respectively, thus making it difficult to draw conclusions that generalize to the global population. The remaining studies had larger sample sizes, however, a significant number of dropouts were observed. Reasons for study withdrawal included treatment side effect, failure to follow-up, and reasons unexplained. In addition, Gordin et al. (2002) excluded subjects with pure tone averages in the unaffected ear of 40dB or more from final analysis. This decision was made without justification, so one must question why the authors opted to include these subjects in the study only to exclude them from final analysis. In general, it is unknown what effect inclusion of these subjects in data analysis may have had on study results and conclusions. Lastly, two studies recruited all subjects from one source. This minimizes daily dietary and routine differences between subjects, therefore, minimizing differences in individual magnesium levels. This allows investigators to make better comparisons between subjects; however, this affects the overall ability to generalize the results.

In accordance with Robyn Cox's (2005) adapted hierarchy of evidence levels, all of the reviewed studies were ranked a level 2. Despite this relatively high ranking, there are procedural decisions that may have affected result validity. Firstly, one must consider when outcome measures were recorded and if additional follow-up was completed. Gordin et al. (2002) calculated outcome measures using an audiogram obtained one-month post treatment, whereas Nageris et al. (2004) and Attias et al. (1994) measured hearing thresholds immediately following treatment cessation.

Additional follow-up was not completed in any of the aforementioned studies. Attias et al. (2004) investigated temporary threshold hearing damage. Outcome measures were obtained immediately after noise exposure and subjects were followed until thresholds returned to baseline measures. It is critical that outcome measures be obtained directly following treatment cessation and that follow-up continue at regular intervals after experiment completion to evaluate the overall stability of the hearing outcomes. Without such follow-up measures there is no way to know the true effectiveness of the treatment.

Because all studies minimally obtained pure tone thresholds it was possible to readily compare between all studies in this review. However, in addition to pure tone thresholds, Attias et al. (2004) also used tympanometry, acoustic reflexes, and click-evoked otoacoustic emissions, thus defining a more accurate picture of auditory system status. It is recommended that future studies use these additional diagnostic tests during subject selection and pre and post treatment assessment. With this information investigators can better exclude subjects who do not meet study inclusion criteria, such as those with normal hearing thresholds, but absent acoustic reflexes indicating complications elsewhere in the auditory system. By defining a more accurate picture of the auditory system status researchers will be able to reduce differences between subjects and draw stronger conclusions focusing on the effects of the magnesium treatment.

In terms of actual supplementation, it was difficult to make comparisons between the studies as different dosages and means of administration were used. None of the studies provided a rationale to justify the amount of magnesium that was given to each subject. Further research needs to be completed to determine dose response curves and best means of magnesium administration.

Finally, the greatest area of criticism encompassing all of the reviewed studies is related to the control of additional factors affecting auditory system status and magnesium metabolism. One of the two studies investigating noise-induced hearing damage diligently excluded subjects with abnormal hearing thresholds and/or a history of noise exposure or disease affecting auditory system function. The other failed to question subjects about disease history. Both studies used younger individuals between the ages of 16 and 37, therefore, lessening the probability of any effects of presbycusis. In the studies investigating idiopathic sudden sensorineural hearing loss, subjects who experienced diseases that could cause hearing loss, including Meniere's disease and the mumps, were excluded; one study also excluded those with a history of occupational noise exposure, while the other failed to do so. The subjects in these studies ranged in age from 22 to 75. No attempt was made to account for the effects of presbycusis. Further research must be completed to determine if the effectiveness of magnesium supplementation is affected by auditory system status prior to treatment. In addition bodily magnesium levels and processes that effect magnesium metabolism should also be considered when comparing subjects within and between studies. It is possible that subjects with naturally higher magnesium levels may benefit less from supplementation and vice versa. Normal blood biochemistry, kidney function, and electrocardiograms, which are known to affect magnesium metabolism, were inclusion criteria in only half of the studies.

Despite the limitations associated with the reviewed studies, some important trends emerged. All four studies reported that relative to the control group, the magnesium treatment group showed a more positive result. A greater proportion of individuals diagnosed with idiopathic sudden sensorineural hearing loss had improved hearing thresholds and an overall greater magnitude of improvement when treated with magnesium. Of the individuals exposed to noise, those who received magnesium treatment experienced less severe temporary and permanent threshold shifts. It should also be noted that only one study reported subjects who dropped out due to side effects associated with the magnesium treatment. No other study reported significant side effects. Lastly, Gordin et al. (2002) made an important observation regarding treatment commencement. Subjects in their study began treatment anywhere within a two-week period following symptom emergence. The authors found that those who began treatment earlier were more successful.

Although these trends sound very promising, one must remember the aforementioned procedural shortcomings. In order to reduce these concerns it is recommended that future studies include the following experimental procedures: (1) completion of a thorough case history to exclude subjects with occupational noise exposure, disease affecting auditory system status, and abnormal blood chemistry or magnesium metabolism, (2) completion of a thorough blood biochemistry analysis to determine pretreatment bodily magnesium levels (3) control for the effects of presbycusis by threshold matching between the control and treatment groups or by using a younger population of subjects, (4) recruitment of a larger and more diverse population of subjects, (5) completion of outcome measures directly after treatment cessation and follow-up measures at regular intervals to monitor results/recovery stability, (6) definition of dose response curves to determine proper amount of supplementation and best means of administration (7) when studying NIHL, control for noise exposure differences by obtaining accurate measures of exposure history during experimental testing using a dosimeter or by using an uniquely

controlled population such as that used by Attias et al. (1994). In general, a prospective, randomized, double-blind, placebo-controlled experimental design is advised using the aforementioned recommendations.

Conclusion

The overall conclusion of this review is that magnesium supplementation is generally associated with a reduction in hearing damage caused by noise exposure and/or idiopathic sudden sensorineural hearing loss in adults. While this review appears to support magnesium supplementation as an innovative and immediate treatment for hearing loss, one must consider the procedural limitations and shortcomings that were highlighted. It is recommended that further research be completed to gather stronger evidence to support magnesium supplementation for the treatment of sensorineural hearing damage prior to beginning clinical trials.

References

Altura, B.M., Altura, B.T., Gebrewold, A., Ising, H. & Gunther, T. (1992). Noise-induced hypertension and magnesium in rats: relationship to microcirculation and Ca. *Journal of Applied Physiology, 72,* 194-202.

Attias, J., Weisz, G., Almog, S., Shahar, A., Wiener, M., Joachims, Z., Netzer, A., Ising, H., Rebentisch, E. & Guenther, T. (1994). Oral Magnesium Intake Reduces Permanent Hearing Loss Induced by Noise. *American Journal of Otolaryngology*, *15*(1), 26-32.

Attias, J., Sapir, S., Bresloff, I., Reshef-Haran I. & Ising, H. (2004). Reduction in noise-induced temporary threshold shift in humans following oral magnesium intake. *Clinical Otolaryngology & Allied Sciences*, *29*(6), 635 – 641.

Byl, F.M. (1984). Sudden hearing loss: eight years' experience and suggested prognostic table. *Laryngoscope, 94,* 647-661.

Gordin, A., Goldenberg, D., Golz, A., Netzer, A. & Joachims, H.Z. (2002). Magnesium: A new therapy for idiopathic sudden sensorineural hearing loss. *Otology & Neurotology*, *23*, 447-451.

Guenther, T., Ising, H. & Joachims, Z. (1989). Biochemical mechanisms affecting susceptibility to noise-induced hearing loss. *American Journal of Otology, 10,* 36-41.

Ising, H, Handrock, M., Gunther, T., Fischer, R. and Dombrowski, M. (1982). Increased noise trauma in guinea pigs through magnesium deficiency. *Archives of Otorhinolaryngology, 236*, 139-146.

Joachims, Z., Babisch, W., Ising, H., Gunther, T. & Handrock, M. (1983). Dependence of noise-induced hearing loss upon perilymph magnesium concentration. *Journal of the Acoustical Society of America, 74*, 104-108.

Joachims, Z., Ising, H. & Gunther, T. (1987). Noise-induced hearing loss in humans as a function of serum Mg concentration. *Magnesium Bulletin*, *9*, 130-131.

National Institute on Deafness and Other Communication Disorders. (2009). Hearing, ear infections, and deafness: Diseases and Conditions. Retrieved from http://www.nidcd.nih.gov/health/hearing/

Nageris, B.I., Ulanovski, D. & Attias, J. (2004). Magnesium treatment for sudden hearing loss. *The Annuls of Otology, Rhinology & Laryngology, 113*, 672-675.

Scheibe, F., Haupt, H. & Vlastos G. A. (2000). Preventative magnesium supplement reduces ischemia-induced hearing loss and blood viscosity in the guinea pig. *European Archives of Otorhinolaryngology*, *257*, 355-361.

Shiraishi, T., Kubo, T., Okumura, S., Naramura, H., Nishimur, M., Okusa, M. & Matsunaga T. (1993). Hearing recovery in sudden deafness patients using a modified defibrinogenation therapy. *Acta oto-laryngologica Supplementum, 501*, 46-50.

Spoendlin, H. (1962). Ultrasound features of the organ of Corti in normal and acoustically situated animals**.** *Annals of Otology, Rhinology and Laryngology, 71,* 657-677.

Thorne, P.R. & Nuttall, A.L. (1987). Laser Doppler measurements of cochlear blood flow during loud sound exposure in the guinea pig. *Hearing Research*, *27,* 1-10.

World Health Organization. (2009). Deafness and hearing impairment. Retrieved from http://www.who.int/mediacentre/factsheets/fs300/en