Critical Review: Is the use of antioxidants associated with improved auditory function in adults with acute onset sensorineural hearing loss?

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This critical review examined the effects of antioxidants on auditory function in individuals with acute onset sensorineural hearing loss in six studies. Study designs included: five prospective, randomized, double blind studies and one retrospective chart review. Overall, the evidence failed to provide support for the clinical administration of antioxidants in adults with acute onset sensorineural hearing loss. However, results were suggestive of a link between antioxidants and improved auditory function. Additional studies involving more subjects to determine appropriate dose response curves for each antioxidant are recommended.

Introduction

The benefits of antioxidants are currently the focus of much human health research, given their free radical scavenging abilities. During normal mitochondrial respiration, reactive oxygen species (ROS) are produced, which can cause cell damage when generated in excess. During normal functioning they are converted to nonreactive molecules by endogenous antioxidants (Darrat et al., 2007). However, disruption of this normally balanced system can result in over production of ROS, thus overwhelming the natural intrinsic defense and resulting in cell injury and death. (Kramer et al., 2006). Administration of exogenous antioxidants can protect cells by scavenging the excess ROS, thereby preventing damage (Darrat et al., 2007). An increase in ROS can result from excessive noise or ototoxic drug exposure resulting in damage to the cochlea. (Darrat et al., 2007). Consequently, there is a growing interest in the use of antioxidants as a means of preventing and treating auditory damage associated with such insults (Darrat et al., 2007).

Noise induced hearing loss (NIHL) is often high frequency and sensorineural in nature and is a result of excessive exposure to sound. Hearing protection has proven beneficial in reducing noise-induced damage to the auditory system. However for some populations (i.e. the military) the use of hearing protection is impractical or unsafe (Fetoni et al., 2009). Therefore NIHL continues to be a common cause of auditory damage. As mentioned above, the overproduction of ROS in the cochlea is the primary mechanism responsible for this damage (Darrat et al., 2007). Animal studies have demonstrated that ROS trigger oxidative stress within the cochlea within a few minutes of noise exposure (Fetoni et al., 2009). The outer hair cells (OHC) of the cochlea are suspected to be the most vulnerable to damage by the ROS, resulting in hearing loss (Kramer et al., 2006). Therefore increasing antioxidant levels within the organ of Corti following exposure to loud noise is a rational approach to treating NIHL. Additional animal studies have investigated this hypothesis with the following antioxidants: Coenzyme Q-Ter® (CoQ-Ter®), a more bioavailable form of Coenzyme Q10, and N-acetylcysteine (NAC). These studies showed reduced cell damage and cell death following excessive noise exposure (Fetoni et al., 2009; Kramer et al., 2006). The success of antioxidants in preventing and treating NIHL in animal models suggests antioxidants may be protective in humans exposed to similar insults (Kramer et al., 2006).

Drug induced hearing loss, like NIHL, is often high frequency and sensorineural in nature. Cisplatin and aminogylcosides (AG), both ototoxic, are widely used in situations where other, less ototoxic drugs are not effective. Therefore finding a protective mechanism against ototoxic damage would greatly benefit a number of patients. Much like NIHL cisplatin administration has been suggested to cause an increase in ROS generation, resulting in damage to the outer hair cells, the cells within the organ of Corti, the spiral ganglion cells and the stria vascularis (Darrat et al., 2007). Weijl et al. (1998) demonstrated a significant decrease in the plasma concentration of various antioxidants during cisplatin treatment. These results suggest that increasing antioxidant levels in the cochlea may be beneficial in reducing cell damage. Animal studies examining the protective effects of vitamin C, vitamin E and NAC produced promising results for the reduction of auditory damage as a result of ototoxic exposure and suggest the need for further studies in human subjects (Weijl et al., 2004; Feldman et al., 2007).

Objectives

The primary objective of this paper was to critically evaluate selected studies that examined the effect of antioxidants on auditory function in patients with acute

onset sensorineural hearing loss as a result of noise exposure, ototoxic drug exposure or as a result of unknown causes.

Methods

Search Strategy

Computerized databases, including PubMed, Medline and SCOPUS were searched using the following search strategy: (auditory OR cochlea OR cochlear OR hearing) AND (antioxidant) AND (oxidative stress). The search was limited to peer reviewed studies in English, conducted on human subjects. The reference section of each of the articles selected was reviewed to locate other articles relating to the topic of interest. A citation search of each of the selected articles was also preformed.

Selection Criteria

Studies included in this critical review were required to examine the effects of antioxidants on auditory function in humans with acute onset sensorineural hearing loss as a result of noise exposure, drug exposure or sudden onset hearing loss with no known cause. Studies included those conducted in North America, Europe, Japan and Israel.

Data Collection

Results of the literature search yielded six articles consistent with the selection criteria: five prospective, randomized, double blind studies, and one retrospective chart review which yielded levels of evidence of 2+ for two articles (Feldman et al., 2007; Fetoni et al., 2009), 2- for three articles (Kramer et al., 2006; Joachims et al., 2003; Weijl et al., 2004) and 4- for one article (Hatano, 2008) based on the level of evidence hierarchy for high quality studies (Cox, 2005).

Results

Noise Induced Hearing Loss

Prospective, randomized, double blind study #1. Fetoni, Garzaro, Ralli, Landolfo, Sensini, Pecorari, Mordente, Paludetti and Giordano (2009) looked at the protective effects of CoQ-Ter® in preventing auditory damage caused by NIHL in twenty young adult male students with normal hearing. CoQ-Ter® is a multi-composite formulation of Coenzyme Q_{10} that is highly soluble, thus increasing its bioavailability while retaining its antioxidant properties. Participants were randomly assigned to a group treated with Q-Ter® (200 mg orally once daily) for seven days prior to noise exposure (n=10) and a second group treated with a placebo following the same schedule (n=10). Both groups were exposed to fifteen minutes of white noise at a level of 90 dB HL. Auditory function was assessed in a sound treated booth using conventional pure tone audiometry and distortion product otoacoustic emissions (DPOAE). Both measures were completed before, and 1 h, 16 h and 7 and 21 days after sound exposure.

Comparison between the CoQ-Ter® group and the control group using a 3-way repeated measures ANOVA revealed a statistically significant interaction effect (treatment group x test time) ($F=17.435$, $p<0.001$). In the placebo group DPOAE amplitudes were reduced for f_2 values of 3174 - 6348 Hz at 1 h post exposure and for f_2 values of 5042-6348 Hz at 16 h post exposure. The CoQ-Ter® treatment group did not show a reduction in DPOAE amplitudes at any frequency, indicating that little or no outer hair cell damage occurred during the noise exposure. Audiometric measures did not reveal a significant difference between the CoQ-Ter® group and the placebo group, indicating the damage incurred during noise exposure was not great enough to cause threshold shifts in either group. The DPOAE results suggest that CoQ-Ter® may have a protective effect against auditory damage in patients exposed to loud noise. These results need to be interpreted with caution given the unrealistic, laboratory-like setting in which the results were obtained.

Prospective, randomized double blind study #2. Kramer, Dreisbach, Lockwood, Baldwin, Kopke, Scranton and O'Leary (2006) investigated whether a single dose of NAC could prevent temporary auditory changes evoked by exposure to loud music in young adult participants with normal hearing. Participants were randomly assigned to a group treated with NAC (900mg) thirty minutes prior to noise exposure (n=15) or a group treated with a placebo following the same schedule (n=16). Both groups were exposed to two hours of loud music at a nightclub. Participants were split into groups of four and one participant from each group was issued a dosimeter to record the average level (dBA) of noise exposure over the two hours. Pure-tone thresholds and DPOAEs were collected before and immediately after noise exposure.

Temporary threshold shift (TTS) was calculated by subtracting the pre-exposure threshold from the post-exposure threshold. The repeated measures ANOVA revealed no statistically significant differences in the amount of TTS or the reduction in DPOAE amplitudes between the two groups following noise exposure. The results of this study are inconclusive because the sample size does not provide enough power to determine if an effect is present or not. Therefore studies involving a greater number of participants are required to provide conclusive evidence about the protective effect of NAC

against noise induced auditory damage. Other issues including the therapeutically effective dose of NAC and appropriate dosage schedule need to be determined through large-scale dose-response studies before research in this area can be accurately interpreted.

Drug Induced Hearing Loss

Prospective, randomized, double blind study #3. Weijl, Elsendoorn, Lentjes, Hopman, Wipkink-Bakker, Zwinderman, Cleton and Osanto (2004) investigated the role of supplementation of vitamin C, vitamin E and selenium in the prevention of cisplatin-induced hearing loss in patients undergoing single agent or combination chemotherapy. Forty-eight patients were randomly assigned to a treatment group (n=25) or a placebo group (n=23) following an identical treatment schedule. The treatment group received vitamin C (1000 mg), vitamin E (400 mg) and selenium (100 µg) in a milky beverage taken twice daily, seven days before the onset of chemotherapy until three weeks after cessation. Mean total doses of cisplatin administered to patients were not statistically different between the treatment and placebo groups. Auditory function was assessed using pure-tone air and bone conduction audiometry at the patient's bedside during treatment and in a sound booth following treatment.

Unpaired student's t-tests were used to compare the two groups. No significant differences were found between the treatment group and the placebo group with respect to the decrease in auditory function. The results of this study suggest that vitamin C, vitamin E and selenium are not effective in the prevention of cisplatin-induced hearing loss. However, when patients were divided based on their reduced/oxidized vitamin C ratio, measured the first day of chemotherapy, into those with a ratio greater than or equal to 7.5 and those with a ratio less than 7.5 a significant difference in the amount of hearing loss was observed between the two groups (P=0.017). Those with high ratios experienced less hearing loss. This data suggests a relationship between oxidative stress and the amount of hearing loss. Therefore antioxidants cannot be ruled out as a potential treatment for those exposed to ototoxic drugs. These results need to be interpreted with caution given the high non-compliance with treatment rate. 46% of participants (64% of the treatment group) stopped drinking the milky beverage before the study concluded.

Prospective, randomized, double blind study #4. Feldman, Efrati, Eviatar, Abramsohn, Yarovoy, Gersch, Averbukh and Weissgarten (2007) evaluated the protective effect of NAC against gentamicin-induced ototoxicity in endstage renal disease patients. Forty patients with clinically suspected bacteremia were randomly assigned to receive gentamicin and NAC (600 mg twice daily; n=20) or gentamicin only (n=20). Auditory function was assessed using conventional and high frequency audiometry from 250 to 12000 Hz, 72 hours after initiation of treatment, and 7 and 42 days after cessation of gentamicin treatment. Auditory toxicity was evaluated by the criteria defined by the American Speech-Language-Hearing Association (ASHA).

Fischer's exact test and repeated measures ANOVA were used to evaluate the data. During treatment with gentamicin, ototoxicity developed in 12 patients in the gentamicin only group (60%) and in five patients from the NAC group (25%), resulting in a 41.6% risk reduction in the NAC group (25/60=41.6; P=0.025). At the 7 and 42 day follow up examinations a significant difference in the amount of patients meeting the ototoxicity criteria was observed between the NAC group and the control group (P=0.022; P=0.002). The greatest change in hearing threshold in the control group was noted in the high audiometric frequencies. These results suggest that NAC is effective in reducing the ototoxic effect of gentamicin in patients. However, there is reason to suspect NAC may be more beneficial in these patients than in the general population given the free radical theory of aminoglycoside toxicity and their elevated levels of oxidative stress. Therefore generalizing these results to other populations should be done with caution.

Idiopathic Sudden Hearing Loss

Prospective, randomized, double blind study #5. Joachims, Segal, Golz, Netzer and Goldenberg (2003) evaluated the benefit of vitamin E in the treatment of patients with unilateral idiopathic sudden hearing loss (ISHL). All participants (n=66) received standard therapy with steroids, magnesium sulfate and carbogen. The treatment group (n=33) received vitamin E (400 mg twice daily) in addition to this standard treatment. There was no significant difference in the interval between the onset of ISHL and beginning of treatment between the two groups. Auditory function was assessed using pure tone audiometry, speech reception threshold and speech discrimination. Hearing recovery was determined by hearing gain and recovery rate measures. Hearing gain was defined as the absolute value of the average hearing recovery in decibels at 250 to 4000 Hz. The recovery rate was defined as the hearing gain divided by the difference in initial hearing level between the affected and unaffected ear, multiplied by 100.

When success of treatment was defined as a recovery rate greater than 75% at the time of discharge, the student's t test revealed a significant difference between

the two groups, with more patients in the treatment group showing recovery (p=0.039). Results indicated the greatest success in those with moderately severe hearing loss, suggesting that vitamin E is beneficial in the treatment of ISHL and improves the rate of recovery. However, replication of the results is necessary given the variability in the severity of hearing loss and the spontaneous recovery rate within this population.

Retrospective chart review. Hatano, Uramoto, Okabe, Furukawa and Ito (2008) investigated whether the administration of vitamins E and C are useful in the treatment of patients with ISHL. The medical charts of eighty-seven patients were reviewed to compare those treated with vitamin E (600 mg once daily) and vitamin C (1200 mg once daily) for four weeks in addition to the standard treatment (n=49) and those received the standard treatment alone (n=38). Standard treatment consisted of administration of steroids, adenosine triphosphate disodium (ATP) and vitamin B12. In some patients (n=41) Alprostadil was administered when little or no recovery was observed in an individual in either group. Pure tone audiometry was performed to assess auditory function on the initial visit. The fixed hearing level was defined as the stable hearing level at one month or more after the onset of hearing loss. Hearing function and therapeutic effects were evaluated using the final pure tone average, hearing gain and recovery rate as defined by the Sudden Deafness Research Committee of the Ministry of Health and Welfare, Japan.

Unpaired Student's t tests were used to evaluate the two groups. The final hearing gain and recovery rate demonstrated a statistically significant difference between the two groups, with a more positive outcome observed in the treatment group ($p<0.05$). These results suggest that the combination of vitamin C and vitamin E may be helpful in treating patients with ISHL. As mentioned above these results should be interpreted with caution given the large variability in hearing loss severity and recovery rate in this particular population.

Discussion

Noise Induced Hearing Loss

Noise induced hearing loss is a continuing problem given the safety issues and lack of compliance concerning the use of hearing protection in certain populations. The mechanism(s) by which temporary changes to auditory function occur may be different from the mechanism(s) of permanent disruption of auditory function. Temporary changes may be a result of overproduction of ROS and therefore may be effectively altered with antioxidant treatment. This may not be the case with more permanent damage. Until the mechanism(s) of both types of damage are clearly understood the results of the studies examined here cannot be generalized to those with permanent NIHL.

The study by Fetoni et al. (2009) demonstrated that CoQ-Ter® has a protective effect in preventing damage to the OHC of the cochlea following noise exposure. The study by Kramer et al. (2006) also examined the effect of an antioxidant, in this case NAC, on temporary changes in auditory function following exposure to loud music. The authors did not find NAC to have any protective effects. However, the evidence of this study is inconclusive due to the small number of participants, which did not provide enough power to say conclusively that NAC does not have a protective effect. Extensive work has been completed examining the effectiveness of NAC in animal models with positive results (Kramer et al., 2006). The potential for NAC to be protective in humans should not be ruled out at this time. The results of these studies are inconclusive, but when taken into consideration with animal trials on the same substances there is evidence to suggest that antioxidants may be protective against temporary auditory damage following noise exposure. Further examination of both CoQ-Ter® and NAC with a greater number of participants and the same randomized, double blind, placebo control design are required to conclusively determine whether or not they are protective. Without research on these substances examining those individuals with existing NIHL their effectiveness in this population remains unknown, as it cannot be extrapolated from these studies. Ethical concerns are discussed below and must be considered in the design of such studies.

Drug Induced Hearing Loss

Patients exposed to ototoxic drugs such as AGs and cisplatin are subject to hearing loss as a result of the excessive generation of ROS. These patient populations also have a compromised health status, which may include disrupted renal function and metabolism resulting in altered pharmacokinetics of the antioxidants. This makes it difficult to generalize the results of these studies to other populations.

The evidence from Feldman et al. (2007) suggests that NAC is effective in the treatment of AG induced hearing loss in patients with end stage renal disease. This is promising evidence in the prevention of hearing loss due to AG exposure. However, this population may be at particularly high risk for ROS damage because of concomitant problems such as uremic syndrome, chronic inflammatory state, bioincompatibility of dialysis membranes and solutions, decreased antioxidant

ability due to vitamin C and E deficiency and reduced activity of the glutathione system (Feldman et al., 2007). Therefore, on the basis of the free radical theory of drug induced hearing loss, treatment with antioxidants may be more effective in this population. The results of this study should not be disregarded but caution should be applied when interpreting and applying the results to other populations.

Despite promising data in cisplatin treated animals models Weijl et al. (2004) found that vitamin C, vitamin E and selenium had no protective effect against auditory damage in humans exposed to cisplatin. However, these results are inconclusive given the high noncompliance rate recorded, which resulted in a dropout rate of 64% of the treatment group. The authors did note a correlation between a patient's initial reduced/oxidized vitamin C ratio and the amount of hearing loss they experienced following cisplatin exposure (r=0.326). This correlation suggests that there may be a link between antioxidant level, oxidative stress and prevention of hearing loss encouraging further studies to examine this relationship. These future studies should be similar to those discussed, with a randomized, double blind, placebo controlled design and a large number of participants. Studies like this are required to support the claims of Feldman et al., (2007) and to determine the effectiveness of antioxidants in treating cisplatin induced damage in order to change clinical practice. Ethical issues addressed below need to be considered.

Idiopathic Sudden Hearing Loss

Hatano et al. (2008) and Joachims et al. (2003) both examined the effectiveness of antioxidants in the treatment of ISHL. Both studies indicated that there was some improvement in the outcome of those treated with either vitamin E alone or in addition to vitamin C. There is a great deal of variability in the degree of hearing loss and rate of spontaneous recovery within this population making them a difficult group in which to study an antioxidant's effectiveness. Given this natural variability a large difference in outcomes between the two groups is required to determine whether the antioxidants were involved in the improved auditory function. Neither study achieved a large enough sample size. Therefore they do not have the power to demonstrate clinical significance. The unknown cause of the hearing loss in this population suggests this population is not ideal for this type of research. Antioxidants are thought to be beneficial in the treatment of hearing losses that result from an overproduction of ROS. The mechanism of damage to the cochlea is unknown in ISHL and therefore the therapeutic potential of antioxidants cannot be assumed. Given these reasons, studying the protective effects of antioxidants in the ISHL population will not prove to contribute useful information to the debate on the effectiveness of antioxidants in the treatment of acute onset hearing loss.

Overall Criticisms

A major concern with the research in this area is the lack of large-scale studies examining the dose response curves of the antioxidants in question. Little is known about how the human body processes and reacts to these substances and without this information a therapeutically effective dose and dosing schedule cannot be determined. The absence of known therapeutic doses results in a variety of studies with varying doses and dosage schedules with conflicting and inconclusive results. The dose response curves are also required to determine potential side effects associated with the antioxidants. None of the studies reviewed reported any evidence of side effects but this is inconclusive given that the therapeutic window of each of the antioxidants has not been determined. The dosage required to reduce auditory damage, may also be associated with negative side effects. A dose response curve would address these concerns and improve future studies. CoQ-Ter® and NAC should be the first to be evaluated given their success in animal models.

The method of assessing auditory function varied in the studies evaluated, DPOAEs were not measured in all cases. The OHCs are more susceptible to ROS damage; therefore, to obtain an accurate assessment of auditory damage and residual function, DPOAEs should be measured in all future studies.

There are ethical concerns regarding treatment with antioxidants, particularly in the absence of dose response curves. Concerns regarding the presence of side effects and interactions between antioxidants should be eliminated before further testing occurs. Ethical concerns exist in regards to a participant's exposure to various cochlear insults. Ideal populations would be those exposed to such hazards because of previously existing medical or occupational reasons (ie. patients who require chemotherapy; military personnel).

Clinical Implications

The evidence regarding the effectiveness of antioxidants in the reduction of auditory damage due to acute insults to the cochlea is inconclusive at this time. Clinical practice should not change as a result of the findings. Further research, as outlined above, is needed to give a more accurate picture of the effects of the multiple antioxidants being studied on the human auditory system.

References

Cox, R. (2005). Evidence-Based Practice in Provision of Amplification. *Journal of the American Academy of Audiology,* 16:419-438.

Darrat, I., Ahmad, N., Seidman, K., and Seidman M.D. (2007). Auditory research involving antioxidants. *Current Opinion in Otolaryngoloy and Head and Neck Surgery,* 15:358-363.

Feldman, L., Efrati, S., Eviatar, E., Abramsohn, R., Yarovoy, I., Gersch, E., et al. (2007). Gentamicin-induced ototoxicity in hemodialysis patients is ameliorated by N-acetylcysteine. *Kidney International, 72*(3), 359-363.

Fetoni, A. R., Garzaro, M., Ralli, M., Landolfo, V., Sensini, M., Pecorari, G., et al. (2009). The monitoring role of otoacoustic emissions and oxidative stress markers in the protective effects of antioxidant administration in noise-exposed subjects: A pilot study. *Medical Science Monitor: International Medical Journal of Experimental and Clinical Research, 15*(11), PR1-8.

Hatano, M., Uramoto, N., Okabe, Y., Furukawa, M., and Makaoto, I. (2008). Vitamin E and vitamin C in the treatment of idiopathic sudden sensorineural hearing loss. *Acta Oto-Laryngologica,* 128: 116-121.

Joachims, H.Z., Segal, J., Golz, A., Netzer, A., and Goldenberg, D. (2003). Antioxidants in Treatment of Idiopathic Sudden Hearing Loss. *Otology & Neurotology,* 24:572-575.

Kramer, S., Dreisbach, L., Lockwood, J., Baldwin, K., Kopke, R., Scranton, S., et al. (2006). Efficacy of the antioxidant N-acetylcysteine (NAC) in protecting ears exposed to loud music. *Journal of the American Academy of Audiology, 17*(4), 265-278.

Weijl, N. I., Elsendoorn, T. J., Lentjes, E. G., Hopman, G. D., Wipkink-Bakker, A., Zwinderman, A. H., et al. (2004). Supplementation with antioxidant micronutrients and chemotherapy-induced toxicity in cancer patients treated with cisplatin-based chemotherapy: A randomised, double-blind, placebo-controlled study. *European Journal of Cancer (Oxford, England : 1990), 40*(11), 1713-1723.

Weijl, N.I., Hopman, G.D., Wipkink-Bakker, A., Lentjes, E.G.W.M., Berger, H.M., Cleton, F.J. and Osanto, S. (1998). Cisplatin combination chemotherapy induces a fall in plasma antioxidants of cancer patients. *Annals of Oncology,* 9: 1331-1337.