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THE EFFECTS OF N-ACETYLCYSTEINE ON NOISE INDUCED HEARING LOSS: A SYSTEMATIC REVIEW

Ni Putu Omasih Kiantimi[1*],I Made Yoga[2,] Ni Nyoman Pringga Dewi Astuti[2]

[1]General Practitioner, Windu Husada General Hospital, Bali, Indonesia
[2] Departement of Otolaryngology- Head and Neck Surgery, Karangasem Regional Hospital, Bali, Indonesia

Correspondence Author:
omakiantimi@gmail.com

ABSTRACT

Background: *A preventable cause of sensorineural hearing loss (SNHL) is noise-induced hearing loss (NIHL). An essential factor in the pathophysiology of NIHL is oxidative stress. NAC is associated with its antioxidant and anti-inflammatory activity, which favors the maintenance of a cellular redox imbalance. As such, its potential for treatment relates to several diseases whose origins and progression are linked to oxidative stress.*

The aim: *This study aims to show the effect of N-Acetyl-Cysteine on sensorineural hearing loss.*

Methods: *By comparing itself to the standards set by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, this study was able to show that it met all of the requirements. So, the experts were able to make sure that the study was as up-to-date as it was possible to be. For this search approach, publications that came out between 2008 and 2023 were taken into account. Several different online reference sources, like Pubmed and ScienceDirect, were used to do this. It was decided not to take into account review pieces, works that had already been published, or works that were only half done.*

Results: *In the PubMed database, the results of our search brought up 37 articles, whereas the results of our search on ScienceDirect brought up 38 articles. The results of the search conducted by screening yielded a total 6 articles for PubMed and 1 article for ScienceDirect. We excluded 1 article having ineligible intervention, and 1 article having ineligible outcomes data. In the end, we included five research that met the criteria.*

Conclusion: *We found positive results in most of the studies, N-acetylcysteine showed better effect on reducing hearing loss and increasing hearing recovery in NIHL and the most common adverse events symptoms reported were gastrointestinal.*

Keywords: *N-Acetylcysteine, noise induce hearing loss, deafness, treatment, prevention*

INTRODUCTION

Sensorineural deafness is a reduction in hearing function caused by damage to the vestibulocochlear nerve, the inner ear, especially the organ of Corti, and the auditory perception center in the brain. The four categories of sensorineural deafness are mild, moderate, severe, and total, depending on the severity.[1] Acquired hearing loss can be caused by several environmental risk factors, and one of the most common is exposure to loud noise.[2] The avoidable cause of sensorineural hearing loss is noice-induced hearing loss (NIHL), which is brought on by prolonged exposure to noise. Up to 17% of adolescents in the United States have audiological evidence of non-impairment hearing loss in one or both ears, according to the Centres for Disease Control and Prevention (CDC). This number roughly equates to 40 million persons between the ages of 20 and 69.[3]

In 2017 the prevalence of sensorineural deafness in the United States reached 48 million people or around 20% of the population of the United States in various degrees of severity. Sensorineural deafness is not only suffered by individuals of advanced age but also those of productive age. The National Institute of Deafness and other Communication stated that in 2017 the prevalence of sensorineural deafness at ages 45-64 years reached 18%, while at ages 65-74 years it reached 30%.[4,5] In general, up to 65% of the patients recover hearing to varying extent. The various factors related to the likelihood of the recovery are age, associated features, duration of hearing loss, severity of hearing loss, pattern of hearing loss, and systemic comorbidities.[6] Experimental animal studies with systemic or local antioxidant use have been shown to protect HCs and reduce hearing loss from acoustic trauma. Among the most extensively studied are N-acetyl-cysteine (NAC), methionine, acetyl-L-carnitine (ALCAR), and resveratrol.[3]

N-Acetylcysteine (NAC) is a drug approved by the Food and Drug Administration (FDA) and recognized by the World Health Organization (WHO) as an essential drug.[7] N-acetylcysteine (NAC) is a chemical that contains sulfhydryl and has mucolytic characteristics. It was first invented in 1960 and its application in medicine was first documented in 1967.[8] Since 1969, it has been used clinically to treat cystic fibrosis. Since then, the use of NAC has been extended to chronic obstructive pulmonary disease and paracetamol overdose, and its therapeutic use has continued to grow. In some countries, including the United States, Canada, and Australia, NAC is commonly available as an over-the-counter nutritional supplement, with antioxidant properties and great commercial appeal as a nutraceutical.[7,8] Cysteine is found naturally in meat, fish, grains, dairy, soybean, and egg products. As a nutritional supplement, NAC is found in small amounts naturally in some fruits and vegetables.[8]

The primary role of NAC is associated with its antioxidant and anti-inflammatory activity, which favors the maintenance of a cellular redox imbalance.[7,8] Because of this, its therapeutic potential pertains to a number of illnesses whose genesis and course are associated with oxidative stress.[7] Oxidative stress plays a crucial role in the pathogenesis of NIHL. Under normal conditions, the human cochlea includes several molecules, such as enzymes, reactive transcription, glutathione, and vitamins, which combine to produce an extensive and advanced defence mechanism against oxidative.[9] The purpose of this systematic review is to determine the effect of N-Acetyl-Cysteine on noise induced hearing loss.

METHODS

Protocol

By following the rules provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, the author of this study made certain that it was up to par with the requirements. This is done to ensure that the conclusions drawn from the inquiry are accurate.

Criteria for Eligibility

For the purpose of this systematic review, we compare and contrast therapeutic use of N-Acetylcysteine on noise induced hearing loss. It is possible to accomplish this by researching or investigating the effect of N-Acetylcysteine therapy to improve hearing function, reduce hearing loss, and side effects on NIHL. As the primary purpose of this piece of writing, demonstrating the relevance of the difficulties that have been identified will take place throughout its entirety.

In order for researchers to take part in the study, it was necessary for them to fulfil the following requirements: 1) The paper needs to be written in English, and it needs to determine the effect of N-Acetyl-Cysteine on NIHL. In order for the manuscript to be considered for publication, it needs to meet both of these requirements. 2) The studied papers include several that were published within the last 15 years. Examples of studies that are not permitted include editorials, submissions that do not have a DOI, review articles that have already been published, and entries that are essentially identical to journal papers that have already been published.

Search Strategy

We used "N-Acetylcysteine"; "sensorineural hearing loss", "deafness", "treatment"; and "prevention" as keywords. The search for studies to be included in the systematic review was carried out from November, 2nd 2023 using the PubMed

and ScienceDirect databases by inputting the words: "acetylcysteine"[MeSH Terms] OR "acetylcysteine"[All Fields] OR "n acetylcysteine"[All Fields]) AND "hearing loss, sensorineural"[MeSH Terms] OR "hearing"[All Fields] AND "loss"[All Fields] AND "sensorineural"[All Fields]) OR "sensorineural hearing loss"[All Fields] OR "sensorineural"[All Fields] AND "hearing"[All Fields] AND "loss"[All Fields] OR "deafness"[MeSH Terms] OR "deafness"[All Fields] OR "deafnesses"[All Fields] AND "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields] OR "treatments"[All Fields] OR "therapy"[MeSH Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "treatment s"[All Fields] AND "prevent"[All Fields] OR "preventability"[All Fields] OR "preventable"[All Fields] OR "preventative"[All Fields] OR "preventatively"[All Fields] OR "preventatives"[All Fields] OR "prevented"[All Fields] OR "preventing"[All Fields] OR "prevention and control"[MeSH Subheading] OR "prevention"[All Fields] AND "control"[All Fields] OR "prevention and control"[All Fields] OR "prevention"[All Fields] OR "prevention s"[All Fields] OR "preventions"[All Fields] OR "preventive"[All Fields] OR "preventively"[All Fields] OR "preventives"[All Fields] OR "prevents"[All Fields] AND (y_15[Filter]) AND (clinicaltrial[Filter]) AND (english[Filter]) used in searching the literature.

Data retrieval

After reading the abstract and the title of each study, the writers performed an examination to determine whether or not the study satisfied the inclusion criteria. The writers then decided which previous research they wanted to utilise as sources for their article and selected those studies. After looking at a number of different research, which all seemed to point to the same trend, this conclusion was drawn. All submissions need to be written in English and can't have been seen anywhere else.

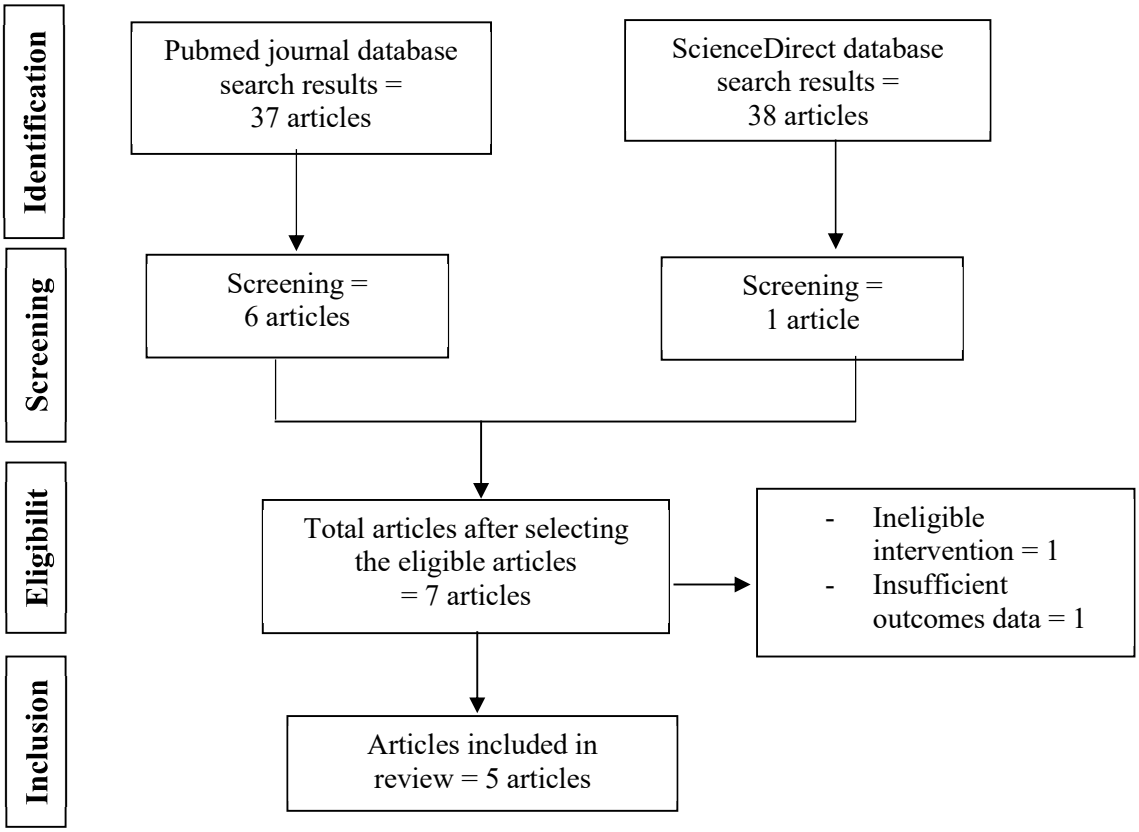

Figure 1. Article search flowchart

Only those papers that were able to satisfy all of the inclusion criteria were taken into consideration for the systematic review. This reduces the number of results to only those that are pertinent to the search. We do not take into consideration the conclusions of any study that does not satisfy our requirements. After this, the findings of the research will be analysed

in great detail. The following pieces of information were uncovered as a result of the inquiry that was carried out for the purpose of this study: names, authors, publication dates, location, study activities, and parameters.

Quality Assessment and Data Synthesis

Each author did their own study on the research that was included in the publication's title and abstract before making a decision about which publications to explore further. The next step will be to evaluate all of the articles that are suitable for inclusion in the review because they match the criteria set forth for that purpose in the review. After that, we'll determine which articles to include in the review depending on the findings that we've uncovered. This criteria is utilised in the process of selecting papers for further assessment in order to simplify the process as much as feasible when selecting papers to evaluate. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review, are being discussed here.

RESULT

In the PubMed database, the results of our search brought up 37 articles, whereas the results of our search on ScienceDirect brought up 38 articles. The results of the search conducted by screening yielded a total 6 articles for PubMed and 1 article for ScienceDirect. We excluded 1 article having ineligible intervention, and 1 article having ineligible outcomes data. In the end, we included five research that met the criteria.

Hearing Improvement

Angeli, et al. (2012)[10] suggested that oral LNAC had important effect on hearing recovery. At 1 month after presentation, combination therapy corticosteroids plus LNAC resulted in a mean pure-tone threshold average (PTA) improvement of 21.7 dB, and in the single therapy group the mean improvement was 14.9 dB (test across groups for mean difference, F ratio = 1.57, p = 0.214). The mean PTA value for the combination therapy group was 37.1 dB (SD, 27 dB), and for the single therapy group was 48.3 dB (SD, 31 dB) (p = 0.15). At 6 months after presentation, combination therapy resulted in a mean final PTA value of 33.6 dB (SD, 24 dB), and the mean final PTA for the single therapy group was 48.2 dB (SD, 30 dB) (p = 0.049). At 6 months, combination therapy corticosteroids plus LNAC resulted in a mean PTA improvement of 26.1 dB, and in the single therapy group the mean improvement was 15.1 dB (test across groups for mean difference, F ratio = 4.16, p = 0.046).

Angeli, et al. (2012)[10] showed that frequency-specific trends were also noted with the combination therapy particularly at 4000 Hz: at 1 month, patients treated with LNAC had a mean threshold improvement of 24.6 dB whereas those who did not take LNAC only had a 6.2 dB improvement (test across groups for mean difference, F ratio = 11.39, p = 0.0014). At 6 months, patients treated with LNAC obtained a mean threshold improvement of 28 dB at 4 kHz whereas those who did not take LNAC had a 6.2 dB improvement (test across groups for mean difference, F ratio = 15.61, p = 0.0002). No statistically significant differences between LNAC groups were found for frequencies 500, 1000, and 2000 kHz. In terms of hearing recovery, the percentage of patients who achieved at least 50% of hearing recovery in the combination therapy versus single therapy groups was 52% (14 of 27) versus 34.5% (10 of 29) (X^2, two-tailed tests, p = 0.189) at 1 month after treatment. At 6 months post-treatment, the percentage of patients with at least 50% recovery was 63% (17/27) for the combination therapy group and 34.5% (10/29) for the single therapy group (X^2, two- tailed test, p = 0.0319. Odds ratio (OR) = 3.23; 95% CI: 1.081, 9.643).

Chen, et al. (2017)[11] showed that the hearing outcome of patients in NAC group had significantly better hearing outcome than in corticosteroid plus plasma expander group (p < .01). NAC group was cured in 11 patients, improved in 21 patients, and unchanged in three patients, accounting for 91% (32/35) improved rate. Compared to 57% improved rate (cured in 10 and improved in 10) in corticosteroid plus plasma expander group.

Hearing Loss

Doosti, et al. (2014)[12] showed linear regression adjusted for hearing threshold before noise exposure and interaction between group and hearing threshold before noise exposure revealed that both ginseng and NAC had preventive effects on hearing loss of both ears at 4, 6, and 16 kHz. Linear regression analysis conducted also revealed that the baseline hearing thresholds was positively associated with the second hearing thresholds (after 14 days) at 4, 6 and 16 kHz ($P <$ 0.001). For each dB increase in before hearing threshold, the estimated after thresholds decreased by 2.86 for NAC, and decreased 1.87 for ginseng at 4 kHz. For each dB increase in before hearing threshold, the estimated after thresholds decreased by 2.54 for NAC, and decreased 1.65 for ginseng at 6 kHz. At 16 kHz, for each dB increase in baseline before hearing threshold, the estimated after thresholds decreased by 2.34 for NAC, and decreased 1.57 for ginseng.

Kopke, et al. (2015)[13] showed that NAC reduced hearing loss. The mean of change in hearing loss over the course of the study was less for the NAC subjects than for the placebo group over the measured audiometric frequencies. Based upon the Sign test, the probability of this occurring by chance for any of the measures is p < 0.001 suggesting NAC reduced hearing loss.

Lin, et al. (2010)[14] showed that noise-induced temporary threshold shift TTS) at high frequency (HF) could be reduced by prophylactic oral administration of the antioxidant NAC at 1200 mg/day for 14 days. Prior to treatment, the pre-shift hearing threshold at HF was 19.3 dB HL, with no difference between the sequences. For all participants exposed to noise, the mean TTS at HF was 2.77 dB after placebo, and 2.45 dB after NAC ($p = 0.03$). These data indicate reduced threshold shift by NAC based on ANOVA for a 2 x 2 crossover design. Effects caused by carry-over and period were non-significant. The TTS at LF were not significantly different ($p = 0.88$) between the post-placebo and post-NAC phases of study.

Adverse Effects

Kopke, et al. (2015)[13] showed that there was no significant difference in the percentage of subjects experiencing an adverse events (drowsiness, ear pain, headache, increased urination, ingestion, stomach ache, tinnitus, vomiting, other) between the NAC and placebo groups (27.4% and 26.7%, respectively, $p = 0.4465$). Similarly, average daily intensity, frequency and severity of adverse events showed no significant differences. The most common adverse events symptoms reported were gastrointestinal. These were uniformly mild and transient. Lin, et al. (2010)[14] showed that there was no adverse side-effects related to NAC or the placebo. Chen, et al. (2017)[11] also showed that none of the patients in NAC group had adverse effects such as nausea, vomiting, headache, rash, etc.

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Intervention	Result
Angeli, 2012[10]	USA	Case-control	27 patients receiving NAC + steroid	Steroid alone vs. steroid + LNAC	This finding suggested that patients treated with oral LNAC in combination with corticosteroid therapy had approximately three times greater chance of hearing recovery than patients who did not receive LNAC. The use of LNAC was most beneficial in the late post-treatment period and in the highest audiometric frequency studied (i.e. 4000 Hz).

Chen, 2017[11]	Taiwan	RCT	35 patients receiving NAC	NAC vs. corticosteroids + plasma expander	This results suggested that NAC may rescue hearing loss from sudden deafness confined to the inner ear like NAC also ameliorates hearing loss from acoustic trauma localized in the inner ear.
Doosti, 2014[12]	Iran	RCT	16 patients receiving NAC	NAC vs ginseng vs. control	This findings concluded oral administration of either NAC (1200 mg/day) or ginseng (200 mg/day) significantly reduced noise-induced temporary threshold shift (TTS) at 4, 6 and 16 kHz frequencies after 14 days. However, the reduction was more prominent in NAC group than in the ginseng group in significant frequencies.
Kopke, 2015[13]	USA	RCT	277 patients receiving NAC	NAC vs. placebo	This findings suggested that a 900 mg dosage of NAC administered three times a day or a 1800 mg dosage of NAC in the morning and a 900 mg dosage of NAC in the evening proved to be safe.

Lin, 2010[14]	Taiwan	RCT	25 patients receiving NAC	NAC then placebo vs. placebo then NAC	This results suggested that NAC is protective against loud continuous noise and demonstrated the feasibility of reducing noise-induced hearing loss using NAC.

DISCUSSION

The purpose of this research was to review studies published after January of 2008 and up to November of 2023 that investigated the effect of N-Acetyl-Cysteine on NIHL. Five identified studies reported that NAC had effects on NIHL. NAC can improve and prevent hearing loss. A number of pathophysiological pathways have been proposed as the causes of SNHL, including vascular disease, viral infection, metabolic disease, autoimmune, and combinations of various variables.[15]

The main function of hair cells is to convert sound waves into electrical messages. Genetics, aging, ototoxic medications, recurrent cochlear infections, and noise exposure are all potential causes of hearing loss. Hair cells, particularly the outer HCs of the basal turn, are subject to oxidative damage and mechanical shearing stresses, which ultimately cause apoptotic cell death. These are the principal mechanisms of hair cell damage that have been identified.[16] There are numerous therapeutic options for SNHL because its etiology is unknown. These include intratympanic steroid injection, calcium channel blockers, antiviral drugs, antioxidants, oral corticosteroids, plasma expanders, and traditional Chinese medicine. Steroid treatment is generally used as the first-line treatment of SNHL However, steroid treatment can have side effects and complications.[17] This systematic review suggested there was no significant adverse side-effects related to NAC, including drowsiness, ear pain, headache, increased urination, ingestion, stomach ache, tinnitus, vomiting, etc.

ROS overproduction occurs when the redox balance between oxidant production and antioxidant defense system activity fails. ROS can directly oxidize macromolecules in physiological conditions, leading to stress signals and cell death in cochlear structures like stria vascularis and hair cells. Increased ROS concentrations can trigger stress signals and scavenge by endogenous antioxidant enzymes. In physiological conditions, ROS increase counteracts oxidative stress, but when ROS concentrations increase, the antioxidant system becomes ineffective, leading to cell death.[2] Among all antioxidants, N-acetyl, L-cysteine (NAC) is probably the most studied molecules to counteract cochlear redox imbalance in NIHL.

Numerous actions of NAC are believed to be advantageous for inner ear cell stress. By initiating programs that cause apoptotic cell death, oxygenated radicals can harm hair cells in the inner ear. As a free radical scavenger, NAC can lower the amount of nitric oxide produced by the cell by promoting the synthesis of reduced glutathione, which in turn lowers the amount of nitrogen radicals that might cause damage. Furthermore, NAC functions as a donor of reduced glutathione, preventing cell death.[18] Studies utilizing less than 1200 mg per day may not demonstrate any appreciable advantage because oral NAC's bioavailability in humans ranges from 4 to 9.1% in one study and from 6 to 10% in another. The half-life of NAC is 6.25 hours, and clearance is both renal and nonrenal, with side effects of nausea, vomiting, and diarrhea.[8]

CONCLUSION

We found positive results in most of the studies, N-acetylcysteine showed better effect on reducing hearing loss and increasing hearing recovery in NIHL and the most common adverse events symptoms reported were gastrointestinal. Population-based studies and larger multicenter randomized controlled trials are needed to aid further investigation and verification of effectiveness and significant side effects

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