Noise-Induced Hearing Loss Treatment: Systematic Review and Meta-analysis

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ABSTRACT

Objective:

To determine the efficacy of steroid and hyperbaric oxygen therapy (HBOT) in the setting of acute noise-induced hearing loss.

Methods:

Systematic review and meta-analysis of noise-induced hearing loss treatment studies that reported on patients who (1) reported individual frequencies up to 8,000 Hz with mean and SDs; (2) were treated only with steroids ± HBOT; and (3) sustained acute acoustic trauma. The Newcastle-Ottawa Scale was used to assess risk of bias across cohorts. Data sources were Embase, Web of Science, Cochrane Databases (via Ovid EBM Reviews), and PubMed.

Results:

Four studies were of retrospective cohorts and one of a prospective cohort. Only one study examined blast acoustic trauma, and the remaining four examined gunfire acoustic trauma. This meta-analysis used a random-effects model for pure tone average (PTA) (0.5, 1, and 2 kHz) and "high-frequency" PTA (HPTA) (4, 6, and 8 kHz) for the five studies included. Steroid therapy demonstrated a 6.55-dB (95% CI, 0.08-13.17 dB) PTA ($n = 55$) improvement and a 9.02-dB (95% CI, 1.45-16.59 dB) HPTA ($n = 71$) improvement. Steroid with HBOT demonstrated a 7.00-dB (95% CI, 0.84-13.17 dB) PTA ($n = 133$) improvement and a 12.41-dB (95% CI, 3.97-20.86 dB) HPTA ($n = 150$) improvement. According to our statistical analysis of the pooled studies' heterogeneity, there was moderate inconsistency in the cross-study results of both treatment groups.

Conclusion:

Steroids with or without HBOT appear to improve both low and high hearing thresholds following acoustic trauma. Future studies will require inclusion of control groups, precise definition of acoustic trauma intensity and duration, and genetic polymorphisms.

INTRODUCTION

Noise-induced hearing loss (NIHL) is defined as temporary or permanent sensorineural hearing loss from high-intensity continuous or impulse acoustic insults.[1,2] In the military population, routine exposure to blasts or firearm discharge during training and/or combat makes hearing loss one of the most prevalent DoD disabilities.[3] More broadly, NIHL is the most common occupational disability, impacting 16% of the world's population.[4] Tinnitus and cognitive impairment are secondary effects, which can cause substantial disruption to the patient.[2,4]

The U.S. OSHA recommends avoidance of impact noise greater than 140 dB. In the military, acute NIHL (aNIHL) may result from a blast exposure, such as a discharge from a weapon muzzle or detonation of an explosive. The 140-dB limit is commonly exceeded in the military environment, with peak sound levels of weapons reaching 150-160 dB.[5,6] Therefore, in many situations, prevention simply may not be possible to the extent necessary to protect hearing.

Noise-induced hearing loss is a function of sound energy duration, intensity, and genetic polymorphisms modifying the cochlear injury response.[3] Recovery of thresholds within 24 hours is defined as a temporary threshold shift (TTS).[2] Temporary threshold shift can be up to 50 dB but recovers within 1 month. However, permanent threshold shift (PTS) does not return to baseline. In either case, there must be at least a 10-dB shift in one or more frequencies. Impulse and continuous noise can cause TTS and PTS. Impulse noise is typically of high intensity and short duration, measured on a scale of milliseconds. Impulse noise is common in explosions or firearm discharge. Continuous noise is much longer in duration measured on the order of hours to days and is usually less intense (i.e., <90 dB).[7] Additionally, if noise is constant or results in repeated TTS, this can result in PTS.[2]

Blast pressure waves disrupt the organ of Corti,[5] inducing permanent loss of hair cells, spiral ganglion neurons, and

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afferent synapses.[8] Intense noise exposure induces a robust inflammatory response with production of inflammatory cytokines and mobilization of immune cells.[9] Additionally, NIHL increases cellular activity, causing metabolic stress that can lead to local hypoxia and apoptosis of hair cells.[10]

Multiple treatment modalities have been tried in patients with aNIHL.[5,8,10–16] Similar to treatment of idiopathic sudden sensorineural hearing loss (SSNHL), local or systemic steroids[9] and hyperbaric oxygen therapy (HBOT)[17] are commonly implemented to address inflammatory and hypoxic[10] post-injury conditions. However, despite the high prevalence of aNIHL in multiple populations, no clinical practice guidelines or consensus statements exist as they do for the treatment of idiopathic SSNHL.[18] Given this large gap in the recommendations for treating aNIHL, we proceeded to design and conduct a systematic review and meta-analysis of the literature to determine the efficacy of steroids and HBOT for hearing recovery following aNIHL.

METHODS

Search

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[19] guidelines were followed in the design and execution of this study. A medical librarian performed searches in Embase, Cochrane Databases (via Ovid EBM Reviews), and PubMed on April 14, 2020. No date limit was imposed. Earliest article was from 1953. The literature search included a combination of keywords and appropriate subject headings to retrieve all articles relevant to aNIHL and treatment. Results were limited to human studies published in English. The final results were exported to Covidence (covidence.org), an online systematic review software tool. In addition, the database Web of Science was utilized to locate additional studies cited in some of the publications found by our initial literature search. To ensure the concept of NIHL was fully captured in the searches, the search included terms such as NIHL, "noise induced hearing loss," "acoustic trauma," and "blast induced hearing loss." To limit the results to articles focused on therapy, our search included terms such as "therapy," "therapeutics," and "management." An example of a PubMed search used is (acute[tiab] OR anihl[tiab] OR subacute[tiab]) AND ((("Hearing Loss, Noise-Induced"[Mesh] OR "noise induced hearing loss"[tiab] OR nihl[tiab] OR "acoustic trauma"[tiab] OR "permanent threshold shift"[tiab] OR "temporary threshold shift"[tiab] OR "blast induced hearing loss"[tiab] OR "occupational hearing loss"[tiab] OR (Blast Injuries[mh] AND Hearing Loss[mh]) OR ("hearing loss"[ti] AND "noise induced")) AND ("therapy" [Subheading] OR "Therapeutics"[Mesh] OR "Otologic Surgical Procedures"[Mesh] OR treatment[tiab] OR therap*[tiab] OR management[tiab]) AND english[lang] NOT ("Animals"[Mesh] NOT ("Animals"[Mesh] AND "Humans"[Mesh])).

Study Selection Parameters

Study inclusion criteria were (1) all study designs were included; (2) NIHL or blast-induced hearing loss was the primary outcome in study patients; (3) patients were administered only systemic steroids with or without HBOT; and (4) data on mean and standard deviation (SDs) frequency thresholds and SDs. Reasonable attempts were made to reach authors of studies if they were selected for full-text review.

Study Quality Assessment

Since the extracted studies were cohort studies, we used the Newcastle-Ottawa Scale to assess quality.[20] This scale includes three criteria, each rated with a star system: (1) study selection, (2) comparability of cohort, and (3) outcome assessment. A study with equal to or more than six stars is considered as high-quality study.

Data Extraction

Web-based Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia) was used to organize titles and abstracts, which were then each separately reviewed by two authors (M.A. and C.E.). Disagreements on studies to include were resolved through discussion. Full texts were thoroughly reviewed for required data. Lastly, references were manually checked for studies potentially missed by our literature search. Extracted data included study design, injury type, treatment regimen, pre-injury and post-treatment frequency mean thresholds and SDs, number of patients, duration of therapy, and follow-up period.

Pure tone average (PTA) (0.5, 1, and 2 kHz) and "high-frequency" PTA (HPTA) (4, 8, and, if available, 6 kHz) weighted mean and pooled SDs were calculated in Microsoft Excel (Microsoft, Redmond, WA). See Tables S1-S7 for individual study calculations and assumptions.

Statistical Analysis

The null hypothesis for this study is that systemic steroids with or without HBOT do not improve post-injury PTA or HPTA. Review Manager Software version 5.4 (Nordic Cochrane Center, Copenhagen, Denmark; Cochrane Collaboration, 2014) calculated pooled mean, SD, and 95% CI. We used a random-effects model for the pooled study data and calculated the inconsistency statistic (I^2) as a measure of heterogeneity, with low, moderate, and high inconsistency defined as 25%, 50%, and 75%, respectively.[21] Forest plots were also generated with Review Manager Software.

RESULTS

Study Selection and Characteristics

Our literature search found a total of 197 records with 69 duplicates, leaving a total of 128 articles to be reviewed. An additional 10 studies were added from Web of Science (Fig. 1). Initial full-text review yielded 68 studies, from

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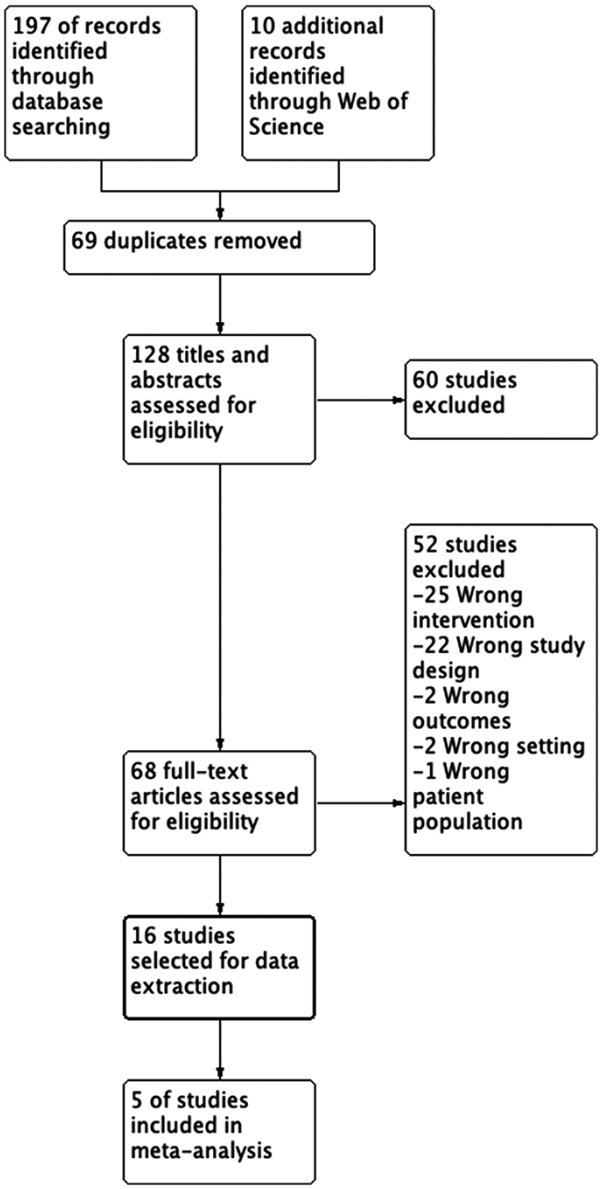

FIGURE 1. PRISMA flowchart for systematic review.

which we selected 16 studies for data extraction. However, upon further review, 11 studies were excluded for one or more of the following reasons: (1) incomplete frequency[22–24] and SD reporting[25]; (2) addition of non-steroid systemic and transtympanic pharmacologic agents[11–13]; (3) single-modality HBOT; and/or[10] (4) wrong study design.[17,26] Thus, five studies were selected that met all our inclusion criteria for meta-analysis.

Four studies examined the impact of gunfire in a military training environment, while only Van Haesendonck et al.[8] reported civilian casualties following blast exposure. There was no measure of noise impulse exposure, and no studies followed the same treatment algorithm. However, all treatments were initiated within 1 month of injury, with the vast majority beginning within 2 weeks of injury. Choi et al.[5] described two cohorts (immediate and delayed steroid administration), which we included separately in our analysis. The systemic steroid therapy dosing utilized was high dose with a duration of at least 7 days. Oya and Tadano[14] did not describe the steroid regimen. Four studies reported cohorts with dual-modality therapy, with two studies[14,15] describing two different HBOT regimens (Table I).

Co-morbid conditions were rarely, and often inconsistently, reported. Only Van Haesendonck et al.[8] specifically reported the Tinnitus Functional Index and Visual Analogue Scale Loudness for tinnitus.[14] They mentioned "subjective symptoms" including tinnitus or aural fullness but did not provide a validated scale.

Quality Assessment

Four included studies were non-randomized, retrospective cohort studies. Van Haesendonck et al.'s study was only the prospective cohort study.[8] All studies except Oya and Tadano[14] lost comparability points because of the absence of control groups. All studies except Oya et al., however, did not have clear inclusion/exclusion criteria unlike the other studies. All cohort studies were deemed high quality according to the Newcastle-Ottawa Scale quality indicator (Supplemental Table SI). However, audiometric data were missing to include word recognition scores and speech-in-noise metrics in all studies. Demographic information of included patients was also missing except from Van Haesendonck et al.,[8] who reported incidence of presence of vertigo and tinnitus in treatment cohort. This absence in all other studies precluded further meta-analysis.

Outcomes

Since aNIHL commonly induces high-frequency hearing loss, we calculated weighted means and pooled SDs as described above for low- and high-frequency PTA (see Tables S2-S8 for raw extracted data). Relative to post-injury PTA, administration of only systemic steroids demonstrated significant mean threshold improvement according to a random-effects model with moderate inconsistency. Similarly, HPTA demonstrated a significant hearing improvement according to a random-effects model with high inconsistency. However, mean improvement between PTA and HPTA was not significant (Fig. 2). Similar to single-modality therapy, random-effects models demonstrated that addition of HBOT to steroid treatment was associated with improved hearing outcomes in both PTA and HPTA groups. There was higher inconsistency within steroid + HBOT group (Fig. 3). Overall, the treatment effects were not significantly different between PTA and HPTA frequencies.

DISCUSSION

Our systematic review and meta-analysis of five studies highlight the role of steroids and HBOT in the treatment of aNIHL.

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TABLE I. Selected Studies in Analysis

Study	Design	Injury	Intervention (number in each arm)	Mean treatment onset days (SD)	Follow-up
Bayoumy et al. (2019)[16]	Retrospective cohort	Gunfire	Group 1: 60 mg prednisolone orally for 7 days ($n = 21$). Group 2: prednisolone with concomitant HBOT 10 sessions at 2.5 atm for 90 minutes ($n = 22$)	Group 1: 5.9 ± 2.7. Group 2: steroids 2.2 ± 2.9, HBOT 4.4 ± 2.7	>3 months (not clearly reported)
Choi et al. (2019)[5]	Retrospective cohort	Gunfire	Group 1: 14 days: 60 mg prednisolone for 10 days, 4-day taper ($n = 21$). Group 2: 10 days: prednisolone: for 5 days, 5-day taper ($n = 8$)	8.48 (4.53)	1 month
Van Haesendonck et al. (2018)[6]	Prospective cohort	Bomb blast	Group 1: methylprednisolone (days 1-3 64 mg per day, days 4-6 32 mg per day, and days 7-9 16 mg per day ($n = 34$)). Group 2: methylprednisolone + HBOT (10 sessions, 2-hour dives, 2.5 atm ($n = 22$))	4.1 (4.3) (86% presented within 72 hours)	1 month
Oya et al. (2019)[23]	Retrospective cohort	Gunfire	Methylprednisolone (course unclear) combined with HBOT using either U.S. Navy TT5 for 6.5 ± 1.1 days or TT9 regimen for 8.5 ± 2.4 days	TT5: 10.3 (7.6), TT9: 27.8 (53.7)	N/A
Salihoglu et al. (2015)[24]	Retrospective cohort	Gunfire	Early group: 90 mg deflazacort, tapering 15 mg in 3-day intervals, complete 18 days with HBOT > 10 session at 2.4 atm for 90 minutes either early ($n = 37$) or delayed ($n = 36$).	Early group: 7.44 (1.97). Delayed group: 18.86 (6.95)	6 weeks

Abbreviations: HBOT, hyperbaric oxygen therapy; TT5, Treatment Table 5; TT9, Treatment Table 9.
TT5: Dive to 180 kPa, then dive to 90 KPa, with interspersed 5 minute intervals of air breathing. Time for this takes 2 hours and 15 minutes.
TT9: Dive to 135 kPa. Time for this 1 hour and 45 minutes.

From the qualitative and quantitative review of these studies, we drew five conclusions that have the potential to help the management of current patients as well as to inform the design of more robust studies and trials. First, many of the regimens reported here mirror the commonly used treatment courses described in the recently updated guidelines for idiopathic SSNHL.[14] Less treatment variability could reduce outcome heterogeneity and broaden the number of studies to include for future analysis. For example, we had to exclude three studies because of the addition of rheologic and presumed antioxidant agents.[11–13]

Second, only Oya and Tadano[14] provided hearing outcomes for untreated patients. Having these data is critical to assess the rate of spontaneous recovery and to determine the true effect of treatment. Bayoumy et al.[16] attempted to control for TTS in their analysis by conducting a "subgroup analysis." Inclusion of a control cohort in the design of future studies would allow for additional quantitative results, such

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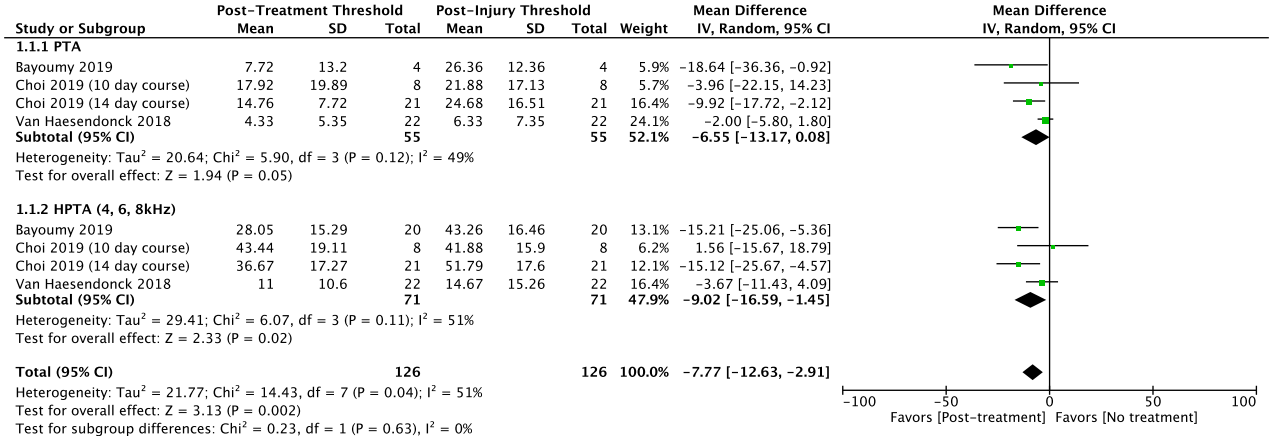

FIGURE 2. Meta-analysis of studies assessing steroid therapy at low and high frequencies following acoustic trauma. HPTA, pure tone average of 4, 6, 8 kHz; PTA, pure tone average of 0.5, 1, 2 kHz; SD, pooled SD.

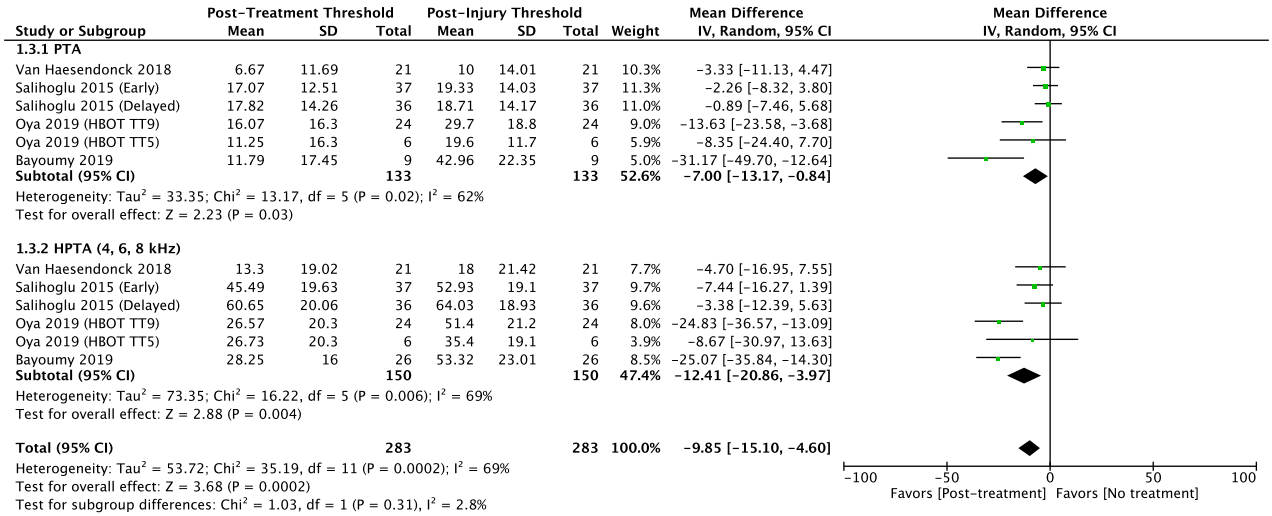

FIGURE 3. Meta-analysis of studies assessing steroid and HBOT therapy at low and high frequencies following acoustic trauma. HBOT, hyperbaric oxygen therapy; HPTA, pure tone average of 4, 6, 8 kHz; PTA, pure tone average of 0.5, 1, 2 kHz; SD, pooled SD.

as calculation of odds ratios after treatment exposure. In our unpublished observations in the DoD, NIHL does not improve in about 50% of patients. Regardless, future studies will need to have a control arm for robust conclusions.

Third, aNIHL is associated with several disabling conditions, including tinnitus and cognitive impairment.[4,16] Only Van Haesendonck et al.[8] reported Tinnitus Functional Index and Visual Analogue Scale Loudness for tinnitus. Future studies should include this in their analysis as an additional measure of a given treatment's efficacy in improving patient outcomes. Additionally, accounting for the so-called "hidden hearing loss" or cochlear synaptopathy[27–29] represents an important patient group that may otherwise be excluded purely due to audiometric parameters.

Fourth, inherent to aNIHL is the wide range of injury patterns that can lead to SSNHL. Many of the studies we examined were from military populations exposed to firearm discharge during training. Given the retrospective nature of most of these studies, the magnitude and duration of noise exposure were not available. Defining magnitude and spectral features of noise is important. For example, continuous noise exposure may eventually result in a PTS, whereas a single substantial noise exposure can result in immediate PTS.[2]

Finally, in addition to the variability of noise exposure, genetic polymorphisms are an important determinant of aNIHL outcomes. Genome-wide association studies of U.S. Marines with well-defined noise exposure from small arms training identified single-nucleotide polymorphisms in genes involved in the regulation of apoptosis, oxidative stress, and potassium metabolism.[4] Recently, analysis of serum[30] and salivary[31] microRNA from factory workers identified several microRNA sequences associated with aNIHL. This emerging evidence should be considered in the design of future studies to further improve the characterization of cohorts and to identify appropriate treatment strategies.

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CONCLUSION

Acute NIHL may be treated with early, high-dose oral steroids and, if possible, HBOT. Future studies should be multi-center randomized controlled trials with complete audiometric data, exact treatment regimens, and extended follow-up. Given the heterogeneity of acoustic trauma sources, study design should be based upon noise exposure as well as individual genetic polymorphisms. In addition to hearing threshold recovery, we recommend comprehensive measurement of vertigo and tinnitus outcomes as these have significant quality-of-life impact. Additionally, these studies should also characterize central auditory processing dysfunction to reflect cochlear synaptopathy. Having sufficient power to study the impact of treatments on the sequelae of acoustic trauma will further improve the quality of life of patients sustaining these injuries.

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SUPPLEMENTARY MATERIAL

Supplementary material is available at *Military Medicine* online.

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CONFLICT OF INTEREST STATEMENT

None declared.

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