ΕΘΝΙΚΟ ΚΑΙ ΚΑΠΟΔΙΣΤΡΙΑΚΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΑΘΗΝΩΝ
ΣΧΟΛΗ ΕΠΙΣΤΗΜΩΝ ΥΓΕΙΑΣ
ΤΜΗΜΑ ΙΑΤΡΙΚΗΣ

ΜΕΤΑΠΤΥΧΙΑΚΟ ΠΡΟΓΡΑΜΜΑ ΣΠΟΥΔΩΝ
«ΑΚΟΟΛΟΓΙΑ – ΝΕΥΡΟΩΤΟΛΟΓΙΑ»

ΔΙΠΛΩΜΑΤΙΚΗ ΕΡΓΑΣΙΑ

«ΣΥΣΤΗΜΑΤΙΚΗ ΑΝΑΣΚΟΠΗΣΗ ΤΗΣ ΧΟΡΗΓΗΣΗΣ ΚΟΡΤΙΖΟΝΗΣ (ΕΝΔΟΤΥΜΠΑΝΙΚΗ Ή ΣΥΣΤΗΜΑΤΙΚΗ) ΣΕ ΑΣΘΕΝΕΙΣ ΜΕ ΑΚΟΥΣΤΙΚΟ ΤΡΑΥΜΑ»

«SYSTEMATIC REVIEW OF CORTISONE ADMINISTRATION (INTRATYMPANIC OR SYSTEMATIC) IN PATIENTS WITH ACOUSTIC TRAUMA»

ΜΙΧΑΛΑΚΗΣ ΗΛΙΑΣ
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ΠΡΟΛΟΓΟΣ

Σε έναν κόσμο βιομηχανικής ανάπτυξης, αστικού θορύβου, πολεμικών επιχειρήσεων, υψηλής πιστότητας ηχοσυστημάτων, συναυλιών και εκρήξεων από τρομοκρατικές επιθέσεις, ο δυνατός ήχος βρίσκεται παντού και αποτελεί έναν διαρκώς αυξανόμενο κίνδυνο για την δημόσια υγεία. Ένας μεγάλης έντασης θόρυβος είναι δυνατό να προκαλέσει ακουστικό τραύμα και οξεία απώλεια ακοής οφειλόμενη σε θόρυβο. Κυριότερη συνέπεια του ακουστικού τραύματος είναι η απώλεια ακοής, διαφορετικής έντασης, που μπορεί να φθάνει στα όρια της κώφωσης.

Σήμερα δεν υπάρχουν διαθέσιμες κατευθυντήριες οδηγίες για την αντιμετώπιση του ακουστικού τραύματος. Έχει δοκιμαστεί πλήθος θεραπειών με αμφίβολα τις περισσότερες φορές αποτελέσματα. Η χρήση κορτικοστεροειδών εφαρμόζεται εδώ και πολλά χρόνια ως μια πιθανώς αποτελεσματική θεραπεία, παραμένουν ωστόσο πολλά ερωτήματα σχετικά με αυτήν.

Αντικείμενο της παρούσας ανασκόπησης είναι η διερεύνηση μέσω της πρόσφατης βιβλιογραφίας της αποτελεσματικότητας της χρήσης στεροειδών στην αντιμετώπιση του ακουστικού τραύματος, καθώς και η διευκρίνηση των βέλτιστων επιλογών όσον αφορά στην επιλογή του φαρμάκου, του δοσολογικού σχήματος, της διάρκειας της θεραπείας, του χρόνου έναρξής της, αλλά και της οδού χορήγησης (συστηματικά ή/και ενδοτυμπανικά).

ΠΕΡΙΛΗΨΗ

Εισαγωγή:

Το οξύ ακουστικό τραύμα (ΟΑΤ) είναι η κλινική οντότητα της άμεσης και εμμένουσας απώλειας ακοής που προκύπτει από έκθεση σε έναν αιφνίδιο και υψηλής έντασης θόρυβο. Δεν υπάρχουν καθορισμένες κατευθυντήριες οδηγίες για την αντιμετώπιση της προκαλούμενης από θόρυβο οξείας απώλειας ακοής. Τα γλυκοκορτικοειδή χρησιμοποιούνται εδώ και χρόνια για την θεραπεία των νόσων του έσω ωτός και φαίνεται πως αποτελούν τη μόνη πιθανώς επωφελή επιλογή για τον ασθενή με ΟΑΤ, καθώς οι στεροειδείς ορμόνες δρουν μέσω διαφορετικών παθοφυσιολογικών οδών μειώνοντας την βλάβη που προκαλεί η υπερέκθεση σε θόρυβο στον κοχλία. Η βέλτιστη διαχείρηση της χορήγησης στεροειδών, σε σχέση με την επιλογή σκευάσματος, την δοσολογία, την οδό χορήγησης, τη διάρκεια και τον χρόνο έναρξης της θεραπείας, δεν είναι επαρκώς καθορισμένα. Σκοπός της παρούσας μελέτης είναι να εκτιμήσει κριτικά τον ρόλο των στεροειδών στην θεραπεία του ΟΑΤ.

Μεθοδολογία:

Χρησιμοποιήθηκε μια λίστα προκαθορισμένων όρων για την ηλεκτρονική αναζήτηση στις βάσεις δεδομένων Medline και Cochrane Library. Κύρια κριτήρια συμπερίληψης ήταν η αγγλική γλώσσα, η δημοσίευση την περίοδο 2005-2019, η απώλεια ακοής λόγω ΟΑΤ και θεραπεία με στεροειδή, κλινικές και προκλινικές μελέτες.

Μελέτες για την απώλεια ακοής προκαλούμενης από θόρυβο λόγω χρόνιας έκθεσης στον θόρυβο, για την οξεία απώλεια ακοής προκαλούμενης από θόρυβο στην οποία όμως εμπλέκεται παθολογία του μέσου ωτός, μελέτες στις οποίες η αντιμετώπιση περιελάμβανε συνδυασμό των στεροειδών με άλλες, μη φαρμακολογικές θεραπείες, όπως η εφαρμογή υπερβαρικού οξυγόνου, με προφυλακτική χορήγηση στεροειδών, μελέτες με απουσία λεπτομερειών για την θεραπεία και τα αποτελέσματα, καθώς και άρθρα των οποίων το πλήρες κείμενο δεν ήταν προσβάσιμο εξαιρέθηκαν.

Αποτελέσματα:

Μετά από συστηματική αναζήτηση, 247 άρθρα ταυτοποιήθηκαν, 232 εξαιρέθηκαν (124 μετά από αφαίρεση των διπλοτύπων, 99 εξαιτίας μη σχετικού περιεχομένου, 10 επειδή δεν πληρούσαν τα κριτήρια επιλεξιμότητας).

Συνολικά, περιελήφθησαν 15 μελέτες στην ποιοτική σύνθεση (6 κλινικές, 9 προκλινικές). Τα αποτελέσματα κάθε μελέτης παρουσιάστηκαν ξεχωριστά, εκτιμώντας την συνολική αποτελεσματικότητα της θεραπείας και όλους τους άλλους παράγοντες που μπορεί να επηρέασαν το αποτέλεσμα.

Συζήτηση:

Τα κύρια σημεία ενδιαφέροντος από τις διαθέσιμες κλινικές και προκλινικές μελέτες είναι:

1. Υπάρχει έλλειψη κλινικών δοκιμών ελεγχόμενων με εικονικό φάρμακο, παρότι οι κλινικές δοκιμές παρουσίασαν πιθανή επωφελή επίδραση των στεροειδών στην θεραπεία του ΟΑΤ. Υποστήριξη της θέσης παρείχε η πλειοψηφία των προκλινικών μελετών.
2. Δεν υπάρχουν στοιχεία για πιθανή διαφορά στην δραστικότητα μεταξύ των διαφορετικών τύπων στεροειδών. Ποιο συχνά χορηγείται η πρεδνιζολόνη σε δόση 60mg από του στόματος και η δεξαμεθαζόνη 5mg/ml ενδοτυμπανικά.
3. Η παρατεταμένη διάρκεια θεραπεία μπορεί να βελτιώσει τα αποτελέσματα
4. Η έγκαιρη αντιμετώπιση φαίνεται πως είναι κρίσιμης σημασίας. Υπάρχουν τεκμήρια πως η πρώιμη έναρξη χορήγησης των στεροειδών βελτιώνει στατιστικώς σημαντικά την αποκατάσταση της ακοής, ειδικά όταν αυτό γίνεται μέσα στην πρώτη ώρα από την έκθεση στον θόρυβο.
5. Η οδός χορήγησης φαίνεται πως δεν επηρεάζει την αποτελεσματικότητα, όμως ο συνδυασμός συστηματικής και ενδοτυμπανικής χορήγησης αποδείχτηκε ανώτερος από την συμβατική συστηματική θεραπεία.

Κύριοι περιορισμοί στις μελέτες που περιελήφθησαν ήταν η απουσία ομάδας ελέγχου στις κλινικές μελέτες, που θα μπορούσε επιπλέον να παράγει μετρήσιμα αποτελέσματα, το μικρό μέγεθος των δειγμάτων και η δυσκολία να καθοριστεί το επίπεδο θορύβου που προκάλεσε το ΟΑΤ.

Συμπεράσματα:
Υπάρχουν στοιχεία για την υποστήριξη της δραστικότητας των στεροειδών στην θεραπεία του ΟΑΤ. Η υψηλή δοσολογία, η άμεση έναρξη της θεραπείας και ο συνδυασμός συστηματικής και ενδοτυμπανικής χορήγησης μπορεί να έχει το βέλτιστο αποτέλεσμα για την αποκατάσταση της ακοής. Απαιτούνται ωστόσο, περισσότερες κλινικές δοκιμές με μεγαλύτερα δείγματα ώστε να μπορέσουν να καθοριστούν κατευθυντήριες οδηγίες για την θεραπεία του ΟΑΤ.

Λέξεις Κλειδιά: αιφνίδια απώλεια ακοής οφειλόμενη σε θόρυβο, ακουστικό τραύμα, θεραπεία, κορτιζόνη, κορτικοστεροειδή, στεροειδή

ABSTRACT

Introduction:

Acute acoustic trauma is the clinical condition of immediate persistent hearing loss after exposure to an impulse and high-intensity noise. There are no definitive guidelines for the treatment of acute noise-induced hearing loss. Glucocorticoids have been long used for therapy of inner ear disease and seem to comprise the only potentially beneficial option for the patient with AAT, since steroid hormones act in several pathophysiological pathways ameliorating cochlear damage induced by noise overexposure. The optimal management of steroid administration, considering the regimen choice, dosage, route, duration and onset of therapy are not well established. The aim of the present study is to critically appraise the role of corticosteroids in AAT treatment.

Methods: A list of predefined terms was used to electronically search the Medline and Cochrane Library databases. Main inclusion criteria were English language; publication during the 2005-2019 period; noise-induced hearing loss due to AAT and steroid treatment; clinical and preclinical studies.

Studies on noise-induced hearing loss due to chronic exposure to noise, acute noise-induced hearing loss involving middle ear pathology, studies on combination of steroids with other, non pharmacological therapies for treatment, such as hyperbaric oxygen administration (HBO), on preventive steroid administration, studies without details of treatment or outcome and articles for which full texts were not obtainable were excluded.

Results:

After systematic search, 247 articles were identified. 232 were excluded (124 after de-duplication, 99 due to irrelevancy with the disease and treatment, 10 due to not fulfilling the eligibility criteria). In total, 15 studies were included in the qualitative synthesis; (6 clinical, 9 preclinical). Results of each study were presented separately, assessing the overall efficacy of treatment and all the other factors that might influence the outcome.

Discussion:

The main points of interest from the available clinical and preclinical studies are:

1. There is a lack of placebo-controlled clinical trial, although clinical studies presented a possible beneficial effect of steroids on AAT treatment. Support was provided by the majority of preclinical studies.
2. There is no evidence of difference in efficacy between various steroid agents. Most common regimens are prednisolone 60mg administered orally and dexamethasone 5mg/ml transtympanically
3. Prolonged treatment duration might further improve outcomes.

4. Early treatment onset seems to be crucial. Evidence suggests that early initiation of steroids significantly improves the final hearing recovery, especially when treatment is offered within an hour from the noise exposure.
5. Route of administration seems to not affect efficacy, however combination of systemic and intratympanic administration proved to be superior over the conventional systemic treatment.

Limitations in the included studies were mainly the absence of control group in clinical studies, which would produce definite and quantitative outcomes, the small size of the samples and the difficulty to determine the noise level and characteristics inducing AAT..

Conclusion:
There is evidence in support of the efficacy of steroid therapy in AAT. High dosage, immediate onset of treatment, combined oral and intratympanic administration may result in the optimal outcome for hearing recovery. Yet, more clinical trials with larger samples are required so that guidelines for AAT treatment can be established.

Keywords: acoustic trauma, acute noise-induced hearing loss, corticosteroid, cortisone, steroid, treatment

ΕΥΧΑΡΙΣΤΙΕΣ

Ευχαριστώ θερμά τον κύριο Μπίμπα, αναπληρωτή καθηγητή και έναν από τους υπεύθυνους του προγράμματος για την ιδιαίτερη έμπνευση και την απεριόριστη κατανόησή του,

τον φίλο και συνάδελφο ογκολόγο Αλέξη Ματίκα για την πολύτιμη βοήθειά του,

την οικογένειά μου για την μεγάλη υπομονή της,

τους φίλους και συμφοιτητές για τη χρήσιμη ανταλλαγή απόψεων.

ΠΙΝΑΚΑΣ ΠΕΡΙΕΧΟΜΕΝΩΝ

ΠΙΝΑΚΑΣ ΑΚΡΩΝΥΜΙΩΝ

ABBREVIATION CHART

AAT.....acute acoustic trauma

ABR..... auditory brainstem response

ANIHL.....acute noise-induced hearing loss

AP.....activator protein

AT.....acoustic trauma

CAM.....cell adhension molecules

CAP.....compound action potential

dB.....deciBell

DM.....dexamethasone

DPOAE.....distortion products otacoustic emissions

GRE.....glucocorticoid response elements

HBO….....hyperbaric oxygen

HL.....hearing loss

IHC.....inner hair cells

IM.....intramuscular

IP.....intraperitoneal

IV.....intravenous

ISSNH.....idiopathic sudden sensorineural hearing loss

ITSI.....intratympanic steroid injection

MLT.....melatonine

MP.....methylprednisolone

NAC.....N-acetylcysteine

NIHL.....noise induced hearing loss

NMDA.....N-methyl-D-aspartate

OHC.....outer hair cells

PD.....prednisolone

p.os.....per os

PTA.....pure tone audiometry

PTS.....permanent threshold shift

ROS.....reactive oxygen species

SGC.....spiral ganglion cell

SPL.....sound pressure level

SRS.....speech recognition score

STAT.....signal transducers and activators of transcription

TCR.....tacrolimus

TTS.....temporary threshold shift

WHO.....World health organization

ΕΥΡΕΤΗΡΙΟ ΔΙΑΓΡΑΜΜΑΤΩΝ ΚΑΙ ΠΙΝΑΚΩΝ

INTRODUCTION

Around 5% of the world's population today, suffers from noise-induced hearing loss caused mainly by industrial or military occupation and recreational activities. (1) Incidence is higher in military personnel; in the United States 2% of the total military personnel is in risk of permanent hearing loss every year, while up to 14% complains about temporary shifts in hearing. According to World's Health Organization (WHO) about 1 in 3 cases of hearing loss may be attributed to noise exposure. Part of this is caused by sudden intense noise and is described as acute noise-induced hearing loss (ANIHL) or acoustic trauma (AT).
Therefore, acute acoustic trauma (AAT) is the clinical condition with immediate persistent hearing loss after impulse and intense noise. (2) But how "intense" is an intense noise?

A usual conversation is conducted at around 40 to 70 decibels (dB). Human auditory system shows the ability to adjust in lower and higher intensity levels, but when the intensity of the sound is over 80 dB a risk for the cochlea occurs, especially for noise of prolonged duration. Even a short period sound can damage the inner ear though; such is the noise of an explosion or of a military firearm, which may produce noise around 160 dB that leads to damage of the inner ear without the proper use of ear protectors and the same can be said for exposure in explosions. Although there is no general consensus, since there may be variability on the distance of the noise source, the type of the noise (blast, pure tone, white noise etc), the direction and so forth, typically a 140 dB noise is considered potentially hazardous for inflicting AAT.

Symptoms of acoustic trauma include hearing loss, aural fullness, tinnitus, recruitment and hyperacousis, difficulty in localizing sounds, especially in unilateral damage, difficulty in hearing in a noisy background and vertigo.
Middle ear may also be damaged, but this review concentrates on inner ear injury.

Pathophysiology of Acute Noise-Induced Hearing Loss

Pure tone audiogram (PTA) is the standard functional measurement of hearing loss in humans.
By this test as measure, noise-induced hearing loss (NIHL) may be separated into 2 sub-types: temporary and permanent hearing loss; each of them presents a different inner-ear pathology.
If the hearing threshold temporarily shifts and then is restored to the pre-exposure level, then this is called temporary threshold shift (TTS), but when there is no restoration, hearing loss is permanent and so is the threshold shift described (PTS). The standard pure tone audiogram of a person with acoustic trauma presents a characteristic sharp notch at 4000 Hz.

Acoustic trauma inflicts hearing loss by 2 major mechanisms, including mechanic and metabolic pathways.
In severe high energy noise, the organ of Corti may be damaged by mechanic destruction even in a short duration of the noise, such as in an explosion (blast mechanisms) (3). When the duration is longer there is an extra metabolic pathway which intensifies the cochlear damage.

Pathology of hair cells and auditory nerve

A satisfactory number and the integrity of hair cells [Inner hair cells (IHC) and Outer hair cells (OHC)], as well of the auditory nerve is necessary for the auditory process to the higher centers.
Temporary threshold shift does not inflict considerable structural damage on the inner ear. In laboratory observations on guinea pigs though, minor changes were observed; distortion and oedema of stereocillia that may cause immobility and consequent inability of OHC and IHC depolarization, as well as oedema in the synaptic region and dendritic contraction, leading to temporary hearing loss that recovers after hours. (4)
Recent studies in mouse models revealed that in TTS although threshold was restored to the initial before the exposure and the IHC and OHC were preserved, there was a late synapses degeneration and loss of neural spiral ganglion cells (SGC) (5) These observations challenge the traditional view that degeneration of spiral ganglion cells and consequently the degeneration of the auditory nerve results only as an aftermath of hair cell loss. This could lead to interesting conclusions in the future, especially regarding the correlation of repeated recreational noise exposure at a younger age with age-related hearing impairment.

High-intensity impulse noise may cause damage to the middle ear, resulting in eardum perforation, ossicular dislocation and therefore conductive hearing loss. (6)
Mechanical damage may be caused in the inner ear too; the typical microscopic observation after a PTS is hair cell and synaptic ribbons loss. (7)
Oedema, dysfunction and subsequent degeneration occurs in inner hair cells. Dendrites, spiral ganglion and Hensen cells have the same fate. This process is progressive and may last for years, resulting in delayed hearing loss.

Molecular mechanisms of Sensorineural Damage in Acoustic Trauma - Oxidative stress

Modern theories about metabolic damage are based on glutamate excitotoxicity and the creation of reactive oxygen species (ROS) which cause activation of apoptosis and necrosis pathways.
ROS occur directly after the exposure to extensive noise and remain up to ten days in the cochlear fluids extending gradually from the basis to the apex and therefore expanding the areas of apoptosis

and necrosis. Glutamate is a neurotransmiter which transfers the signal from the IHC to the dendrites of the SGCs through the synaptic ribbin area. Higher levels of glutamate may overexcite the meta-synaptic cells causing swelling of the dendrites, as well as of the body of the neural cells. This process is called excitotoxicity.

Another metabolic effect of noise is the increase of calcium concentration in OHC, following a high intensity noise impulse. Part of it flows through the calcium channels, while another part increases as a result of intracellular storage release.

Treatment of AAT

Since the supposed pathophysiology of AAT and ANIHL resulting to early or delayed sensory and neural cell loss is complex, a great variety of regiments has been tested in the laboratory to reverse cochlear damage. Antagonists of adenosine and N-Methyl-D-Aspartate receptors, anti-oxidants and Ca^{2+}channel blockers among others were used in preclinical trials. (19)
Neurotrophic agents and N-acetylcysteine have also been tested in animals, as well as vasodilators and glutamate antagonists.

A great number of those agents that were tried in preclinical studies for ANIHL have been found to be realitvely effective in hearing restoration of animals, but few clinical trials presented similar outcome. Most of the agents tried, belonged to the anti-oxidant category and their efficacy on other diseases has already been established.
N-acetylcysteine was clinically tested in soldiers with ANIHL during military training but without definitive results. (20) Contrary to prior experimental and limited clinical positive results, there were no differences in the primary outcomes.
Magnesium was also related to possible effectiveness in ATT attenuation, since a possible association was detected between AT and Mg blood levels, in a prospective study enrolling air force pilots. (19)

Among other non-pharmacological therapies tested in laboratory, the one that was clinicaly tried and is already used as a possible treatment is the Hyperbaric Oxygen therapy (HBO).
Despite the positive results of several articles though, in their systemic review *van der Veen, et al.* studying the effect of HBO treatment of AAT, were able to find only three eligible original studies for the data pool. Their final results were rather inconclusive. (21)

On the other hand, there have been published some studies on the use of combination of HBO with steroids, with positive results regarding hearing recovery. *Lafere et al*. in 2010, studying 68 military

patients suffering from AAT, concluded that the combination of HBO and steroids was better in hearing recovery than steroid treatment alone. (22, 23)
Salihoglou et al. enrolled 48 patients with AAT and treated them with HBO and steroids. The outcomes considering hearing recovery were rather poor, but they found a significant difference when treatment initiation was early. (23)

Steroid treatment

Corticosteroids have been long used for the treatment of hearing loss. They are recommended as first line treatment in inner ear disorders, such as Meniére's disease, sudden sensorineural hearing loss (SSNHL) (25), auto-immune inner ear disease, and in any other hearing or vestibular disorder with a possible inflammation. Predominately administered glucocorticoids today are dexamethasone, prednisolone and methyl-prednisolone.
As already mentioned, there are several studies advocating the positive effect of steroid treatment of idiopathic sensorineural hearing loss administered systematically, intratympanically or in a combination of the two (24) , including systematic reviews and meta-analyses. (25)
Possible common pathophysiological mechanisms between ISSNHL and ANIHL include inflammation, oxidative stress and metabolic changes, therefore similar therapeutic agents and specifically steroids may benefit both ISSNHL and ANIHL patients.

Protective Mechanisms of Glucocorticoids in Cochlear injuries

Glucocorticoids bind to receptors inside the cell, regulating gene expression and protein synthesis. The exact role of steroids in the protection of the inner ear is not yet clear.
There are 2 types of glucocorticoid receptors: type α and type β. Immunohistochemistry research established that type α consist the vast majority (99%) of them; they are extensively identified in the inner ear (8).

Two different pathways are followed during the glucocorticoid exertion: genomic and nongenomic.

Genomic activity is regulated by intra-cellular steroid receptors. The process of binding of the hormone to the receptor causes disconnection, dimerization and translocation of the receptor from the membrane to the nucleus of the cell. (10) (16)
This steroid/steroid-receptor complex either induces or inhibits gene transcription. (11) *Maeda et al.* showed that 12 hours after noise overexposure, various immune-related gene pathways were altered. (12) The researchers administered dexamethasone to this ANIHL model. At 12h they

identified modulation of gene pathways ("cell adhesion molecules" and "cytokine-cytokine receptor interaction") in the immune system, compared with controls.
Several other studies show that dexamethasone regulates ten more genes correlated with hearing function. (12)

The other pathway of action is the non-genomic. It involves a variety different mechanisms. These actions are assosiated with multiple non-specific interactions of steroid hormones with membranic receptors. (17) (18)
For example, research showed that the use of RU486, a glucocorticoid receptor antagonist, improves cochlear damage by binding partialy to glucocorticoid receptors. (13)

Glucocorticoids stimulate the production of antiinflammatory and inhibit the release of proinflammatory cytokines. Cytokines are well documented as inflammatory mediators and are also considered to play this role in cochlear injury too. (14) (15)

OBJECTIVES

Among all therapeutic modalities applied for acute noise-induced hearing loss until now, evidence in favor of steroid administration is still growing, so that they are considered today the appropriate treatment for patients with acoustic trauma.

However, there is no definite consensus on the best management of this treatment.

The reasonable consequent question is how the patient suffering from acute noise-induced hearing loss would receive the maximum therapeutic benefit by the administration of steroids.

Therefore, objectives of this review are to assess steroid treatment for acoustic trauma considering

- overall efficacy
- adequate regimen
- optimal dosage
- time of onset
- route of administration

METHODS

Review of the literature

Search strategy

A review of the published literature regarding cases of acoustic trauma and steroid therapy was performed. A search of the Medline and Cochrane Library databases was conducted until September 2019, using the search terms: ‘acoustic trauma’, ‘acute noise-induced hearing loss’, ‘treatment’, 'steroid', 'dexamethasone', 'prednisolone' in different combinations.

Only English language articles were considered. Articles in languages other than English (German, French, Chinese) were excluded.

Database search included studies published the last 15 years; between 2005 and September 2019. Older articles were excluded.

While the present review is primarily concentrated on clinical studies, experimental researches were complementary included too, in consideration of better understanding the subject.

All studies were reviewed based on available abstracts and complete articles analysis. References of the articles were also screened for potential additional studies.

In case the same author published different articles every time regarding different aspects of the same population, only the latest article was included. When only part of the population was the same and the aim of the study was different articles were also included.

Other exclusion criteria were studies on noise-induced hearing loss caused by chronic exposure to noise; acute noise-induced hearing loss involving middle ear pathology; studies on combination of steroids with other, non pharmacological therapies for treatment, such as hyperbaric oxygen administration (HBO).

Also, as only post-traumatic therapy aimed to be evaluated, studies in which a regimen was administered prior the noise incidence, for prevention, were excluded.

Finally, articles without details of treatment or outcome and studies for which full texts were not obtainable were excluded too.

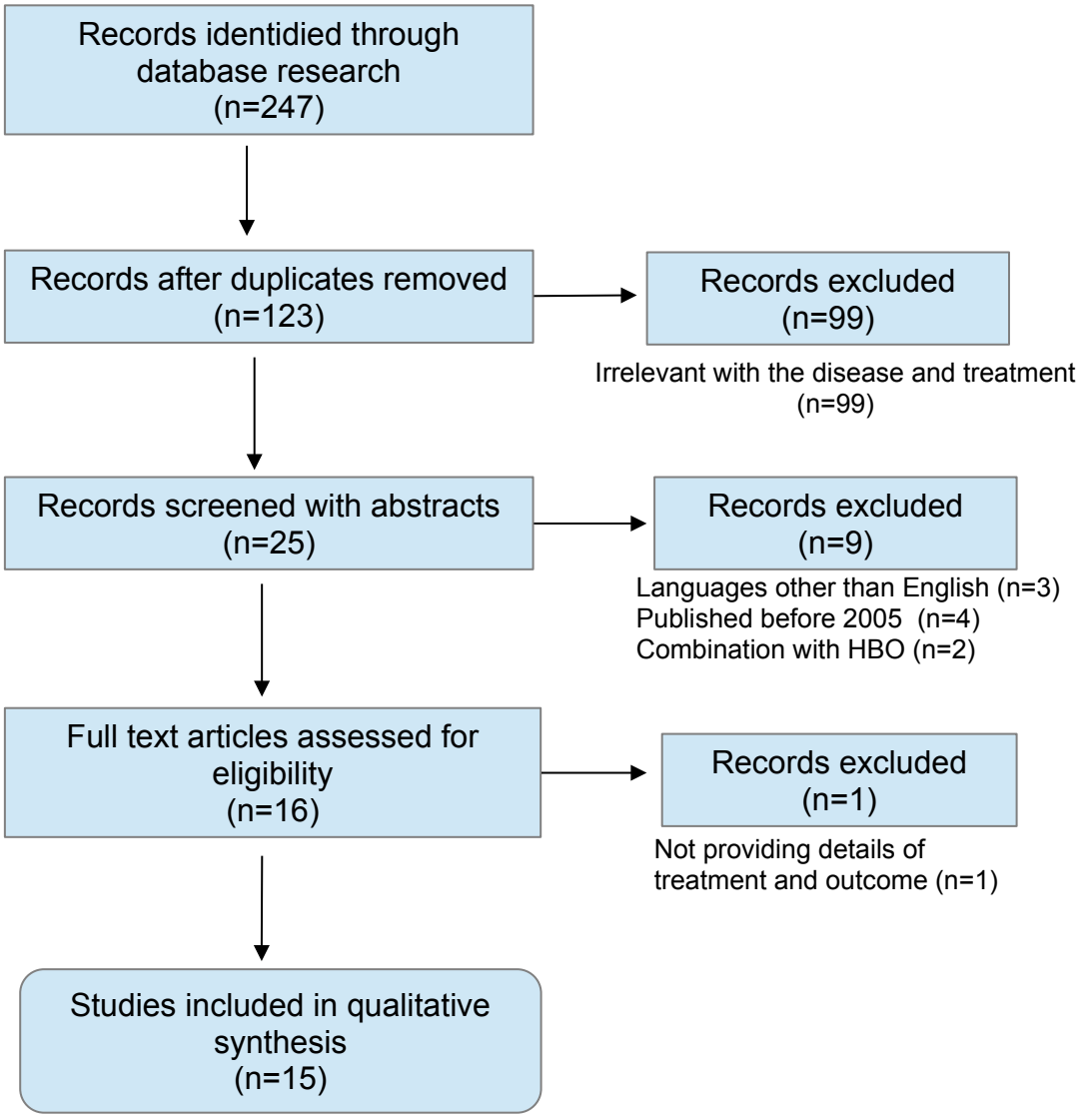
Variables collected included author, publication year, sample size, subjects and source of sounds, treatment and conclusions.

Initial search with the terms “acoustic trauma+steroid+treatment”, “acute noise-induced hearing

loss+steroid+treatment", "acoustic trauma+prednisolone", "acoustic trauma+dexamethasone", "acute noise-induced hearing loss+prednisolone", "acute noise-induced hearing loss+dexamethasone" in PubMed resulted in a total of 247 articles. After deduplication, irrelevant articles were excluded, as well as articles that did not meet the eligibility criteria or were not obtainable.

RESULTS

A total of 15 articles were included in the qualitative synthesis, consisting of 9 preclinical and 6 clinical studies.



Διάγραμμα 1
Flow diagram of the inclusion and exclusion of articles.

Note: After reviewing the full text articles there was concern about a study by *Chang et al*. (38), since as it was mentioned in the material and methods section, part of the population enrolled had already participated in a previous study of the same author. (44) We decided to include the study, since the aim of it was different and the present review is not using statistical analysis, so although inappropriate for quantitative it would be useful for the qualitative synthesis, considering also the rarity of clinical studies on the subject.

Preclinical studies

Mamelle et al. assigned 13 guinea pigs to evaluate ITSI after AAT. Hyaluronic acid (HA) gel with liposomes was loaded with DM (DexP) before the administration.
An AAT was induced during a period from 1h to 2 days. 2 d after the onset, animals were randomly assigned to 4 groups: 1.control 2.gel 3.gel with free DM 4.gel with DM loaded to liposomes.
ABR was performed in days -2, 0, 7, 30.
After 7 days, hearing levels were restored in the control group at all frequencies except 8000 Hz, but not in the 3 groups that received gel injection. 30 days after the exposure, all animals recovered normal hearing, except at the 8000 Hz frequency, concluding that local DM especially administered with gel did not improve HL. (47)

Gumrucku et al. used 16 female Wistar albino rats. The animals were divided into 2 groups, each one exposed in a 110 dB noise for 25min.
In Group A was administered intatympanic DM while in Group B 0.09% saline solution (control group). DPOAE performed in days 7 and 10.
There were significant differences on measurements at all frequencies in both day 7 and 10.
IM DM had a positive effect on AAT. (48)

Han et al. used 24 C57BL/6J mice. 18 of them were exposed in 110 dB spl white noise and then divided into 3 groups:
1.Control.
2.Intraperitoneal DM injection group (IP) -3mg/kg/d for 5 days
3.Intraympanic DM injection group (IT)- injections days 1 and 4.
Hearing was tested with DPOAE and ABR and histological examination was performed.
Both IP and IT groups showed recovery in ABR but not in DPOAE.
Light and electron microscopy revealed preservation of the organ of Corti in IP group compared to control. Outer Hair Cells (OHC) were preserved in greater numbers in IT group. (49)

Chi et al. assigned 74 albino guinea pigs and exposed them to high intensity noise (80 impulses with a peak intense level of 167 dB, duration 0.5 ms with 2 s interval).
Animals were sorted into 2 groups, one receiving topical dexamethasone (40mg/ml) and the other, being the control group, saline solution.
ABR was measured for each animal, before and after the day of exposure in days 1 and 21.
Cochlear morphology was examined under microspopy and ondialdehyde and superoxide dismutase concentrations were determined 21 d after treatment. High-performance liquid chromatography was used to determine the pharmacokinetic characteristics of dexamethasone in cochlear perilymph, following topical application. (51)
Three weeks after the onset of treatment in ABR test, animals showed significant attenuation of noise-induced threshold shifts (comparison was made for days 1 and 21, between treated animals and controls).
Spiral ganglion morphology was found normal.
Animals which received DM, were tested with a significantly higher superoxide dismutase concentration and a significantly lower malondialdehyde concentration, post-exposure.
With the use of high-performance liquid chromatography concentration of perilymph was measured in level peak of DM at 5330.522 μg/ml, 15 minutes post-treatment, reduced to 299.797 μg/ml 360 minutes later. (51)

Ozdogan et al. used 16 Wistar albino rats for their trial. The animals were exposed to noise and were sorted into two groups, a study and a control group. IT MP was injected in the first group after the AAT. DPOAE was performed before and after noise appliance.
The test revealed significantly better thresholds for the treated group in the 1st week but no difference in the second. In noise group (control) a higher number of apoptotic cells were identified during microscopical examination. (50)

Bas et al. used 32 Wistar rats, exposed into 120 dB SPL noise for 4 hours. Animals were randomly divided into 3 groups each one administered with a different therapeutic compound: 1.the anti-inflammatory DM, 2. the antioxidant melatonine (MLT) and 3. the immunosuppressant tacrolimus (TCR).
Testing included audiological evaluation with ABR and DPOAE, as well as laboratory studies; cytocochleogram and determination of gene expression. Dexamethasone did not show otoprotective role, in contrast with MLT as well as with TCR, eventually leading to full recovery protecting also from the OHC loss. (52)

Zhou et al. used 55 guinea pigs, categorized into 6 groups after exposed to intensive impulse noise (60 impulses at 165 dB SPL, 0,5 ms duration, 2 sec intervals). MP was administered either

intramuscular (IM) or intratympanic (IT); ABR and post-mortem histology were performed to evaluate the results of this noise.
In ABR, treated animals (both IM and IT) performed better than untreated. During microscopy circa 50% of the appex of the cochlea a major OHC loss was observed. (46)

Sendowski et al used 32 pigmented guinea pigs, exposing them to an impulse noise tauma (170dB SPL peak).
1 week before the experiment, the 2 cochleae of all the animals were implanted with recording electrodes for electrocochleography (ECG). Also, a microcannulation connected to a mini-osmotic pump filled with artificial perilymph was implanted in one cochlea, while the other not. Compound action potential (CAP) was recorded before noise exposure, (53) Then, with microcannulation, the pump was replaced with one with methylprednisolone (MP).
CAP was recorded over a period of 14 d of recovery after the exposure. A histological examination followed.
48 hours the AAT, significant differences were observed in auditory thresholds between implanted and non-implanted animals, for high frequencies, over 8000 Hz (8-22 kHz). After 7 days of recovery, differences between groups decreased and were signifficant only for 19kHz. After 14 days, no signifficant difference was observed between treated and non-treated animals.
Cochleography revealed a significant hair cells loss in the non treated ears, especially for OHC.
The main lesions concerned the 3 to 6kHz frequencies. Signifficant differences (p<0.01 or <0.05) were also observed for the area between 8 and 16kHz. Generally in the non-implanted
ears, missing hair reached about 30% for IHC and 46% for OHC, while for MP treated were about 8% and 16%, which was a statistical significant difference (p<0.05). (53)

Tabuchi et al. aimed to examine the possible therapeutic time window of glucocorticoids. Therefore, they assigned 30 mice and exposed them to a 128 dB SPL, 4 kHz pure-tone for 4 hours. Auditory thresholds were measured with ABR before, immediately after, and 2 weeks after the initial exposure. After that mice were sacrificed and a histological examination was performed.

ABR threshold shifts were significantly ameliorated when MP was administered before or right after the end of the noise, but did not improve when the agent was administered three hours after the signal.
MP was found effective at doses of 30 mg/kg or 100 mg/kg, but failed to achieve the same results at 10 mg/kg. (54)

Author, year	n.	Steroid	Adm route	Tests	Results	Ref.
Mamelle, 2018	13	DM + gel hyaluronic acid	IT	ABR	No improvement (after 48h with gel HA)	[47]
Gumrucku, 2018	16	DM	IT	DPOAE	DM better than control	[48]
Han, 2015	24	DM	IT S (intraperitoneal-IP)	ABR DPOAE Histology	-IT offers protection for OHC synapses -S protects O.Corti	[49]
Ozdogan, 2012	16	MP	IT	DPOAE Histology	Reduced OHC loss. no difference in DPOAE after 2 weeks	[50]
Chi, 2011	74	DM	IT (round window)	ABR Histology	Reduced OHC loss improved ABR	[51]
Bas, 2009	32	DM	S	DPOAE ABR Cytocochliogram Gene expression	DM failed to protect the cochlea. Tacrolimus, Melatonine prevented OHC loss	[52]
Zhou, 2009	55	MP	IT or S (im)	ABR	ABR better in both IT and IM groups than in control -IT protects HC	[46]
Sendowski, 2006	32	MP	IT (mini-osmotic pump)	ECG Histology	-Better results in ECG in day 7. The same in day 14 -Prevention of HC loss	[53]
Tabuchi, 2006	30	MP	S	ABR Histology	-Better results when administered <3h -no difference 3h<	[54]

Πίνακας 1 Summary of the methods and results in acoustic trauma animal model studies testing corticosteroid efficacy

Clinical studies

Chang et al. in 2017 enrolled 19 patients. All of them were male and belonged to military personnel. They refered for acute noise-induced hearing loss, all of them ipsilateral, after exposure to gunshot noise.

The study had strict inclusion and exclusion criteria. Inclusion criteria were: 1.development of hearing loss after gunshot noise exposure; 2. hearing loss confirmed with PTA; 3.average hearing

threshold change 30 dB HL at 2, 4, and 8 kHz; 4.onset of initial treatment 3 days to 2 weeks.
Exclusion criteria were: 1. previous or current history of any otologic disease (otitis media, sudden sensorineural hearing loss, traumatic tympanic perforation, vestibular schwannoma, and Meniere's disease); 2. evidence of perforation of the tympanic membrane, or other trauma of the external auditory canal following exposure to gunshot noise, as determined by otoscopic examination; 3. any medication taken within the first 3 days after onset; 4.history of gunshot noise-related hearing loss; 5. patients who denied ITSI administration. (44)

Patients were divided into 2 groups: 8 of them were administered only with prednisolone (PD) orally, while the rest 11 received PD and intratypanic steroid injection (ITSI).
All patients received oral PD : 60 mg daily, for 10 days with a subsequent sequential tapering for 4 more days (14 total) and oral ginkgo biloba at a dose (40 mg twice a day).
Patients received ITSI every second day for a total of 4 sessions, by injecting the tympanic membrane a desamethasone (DM) 5mg/ml solution.
Statistical analysis was performed using Mann-Whitney and Wilcoxon signed rank test, followed by a multiviriable linear regression analysis.

The results of this study showed that the combined administration of S steroids with ITSI, caused an extra hearing recovery of 11.48 dB. Moreover, although the S (oral) steroids failed in producing recovery at 8 kHz, concurrent therapy achieved hearing gain from 2 to 8 kHz.

Chang et al. published another study in 2018. Part of the population of this was already included in the previous (44). In this retrospective study, there were reviewed patients who underwent combined systematic (oral) and intratympanic steroid treatment.
19 patients were examined, of which 18 presented with unilaterla and 1 with bilateral hearing loss.
Depending on the time of the onset of HL patients were categorized into 2 groups: 1."Early treatment initiation" when treatment initiated between the 3rd and the 7th day and 2."Delayed treatment initiation" for therapy initiating >7 days.

Inclusion criteria were 1. development of hearing loss following exposure to gunshots, artillery fire, or training grenade's simulated explosion; 2. hearing loss confirmed with PTA, involving high-frequency testing; 3. the average hearing threshold change 25 dB HL at 2 to 8 kHz; 4. onset of initialtreatment 3 days to 2 weeks; 5. patients treated with IT+S steroids.
Exclusion criteria were the presence or history of any otologic disease and the intake of any medication within the first 3 days.

Patients received oral PD 60mg for 4 days, gingko biloba 40mg x 2 and ITSI every second day for

a total of 4 times (DM 5mg/ml).
PTA was performed and statistical analysis followed using Mann-Whitney tests and Wilcoxon signed rank test, followed by multivariable linear regression analysis.

In the multivariable linear regression analysis, initial PTA and treatment initiation showed significant associations with the degree of hearing gain (R^2=0.37). Regression coefficient of the initial PTA was 0.37 (p=0.04). The early initiation group presented a aignificantly greater improvement of hearing levels in comparison with the late initiation group (unstandard. Regr. coefficient =12.63, p=0.01) Hearing thresholds at 2000 Hz did not show significant improvements in the delayed treatment initiation group (p=0.07, Wilcoxon signed-rank test). (38)
Treatment was well tolerated by all patients, and there was no significant side effect observed. (38)

Yehudai et al in 2017, aimed in detecting AAT among military personel during the military "Prodective Edge", as well as to assess the effectiveness of hearing protection devices and evaluating the possible benefit of steroid treatment in AAT. Therefore, they included in their study a total of 186 soldiers who were referred for suspected AAT during the military operation and up to 3 months after it.
Out of 186 soldiers presented with hearing complaints after high intensity noise 122 were in duty service, 39 career personnel and 25 reservists. Their mean age of 21.1, 29.2, and 30.4 yr, respectively.

Of them, about half, 92 (49%) were confirmed with hearing loss in at least 1 ear. Out of total 92 with confirmed HL, 21 participants received treatment, while 71 were left untreated. Initial presentation was characterized as "immediate" when the patient was referred 10 days or less after the AAT and "late" from day 11 and after. Treatment included oral PD (1 mg/kg, with a 60 mg maximum) for a mean of 7.8 days.
Only 56 of the patients showed up in the 1 month follow up.
Statistical analysis was performed using x^2 test, Fischer's exact test and student's independent samples t test.

Hearing impairment was significantly commoner in unprotected patients, when compared with protected 62% versus 45% (p=0.05). Tinnitus also, was more common in the unprotected group when compared with protected (75% vs 49%, p=0.05), whereas vertigo was rare for both groups (5% vs 2.5%, p=0.05).
Air and especially bone-conduction hearing thresholds significantly improved in the post-treatment PTA, when compared with untreated patients (p <0.01). (39)

Choi et al. (2018) retrospectively reviewed the cases of 29 patients with a diagnosis of unilateral AAT.

Inclusion criteria were unilateral HL following a gunshot noise, high frequency PTA at 2, 4 and 8 kHz ≥ 25 dB HL at initial audiometric test and exclusion criteria were a history of otological disease or HL due to prior exposure to gunshot noise and previous AAT, as well as bilateral HL.

Patients were divided into 2 groups and received oral steroid therapy.

The two groups differed in the duration of treatment in days. Group 1 (n=21) received a 14 day course of treatment; 60 mg PD per day for the first 10 days, tapering down over days 11–14. Group 2 (n=8) received PD for 10 days in total: 60 mg for the first 5 days, tapering off every day until day 10. (28) Therefore, the total dosage of PD received by the patients of group 2 patients was less than that intaken by patients of group 1.

Subjects were evaluated with PTA and statistical analysis using the Mann–Whitney U test and Fisher's exact test was performed, as well as The Wilcoxon signed-rank sum test and a multivariable linear regression analysis.

In the first group (14d. course) post-treatment hearing threshold revealed a significant improvement in all frequencies ($p<0.05$), whereas second (10d.) did not show a similar improvement.

The multivariable linear regression analysis was performed considering hearing gain as a dependent, continuous variable. The duration of therapy and the pre-treatment PTA had a significant correlation with the amount of hearing gain ($R^2 = 0.51$, $p < 0.001$). Regression coefficient of initial PTA was 0.45 ($p = 0.004$). Concluding, prolonged treatment (14d, 10+4) was superior to short treatment (10d.5+5) in terms of hearing gain (unstandardised regression coefficient =9.90, p =0.03) (28).

Zhou et al. investigated the early intratympanic steroid injection (ITSI) in patients with delayed treatment of ANIHL. Their study aimed to evaluate the combination of systematic (oral) steroid treatment with a ITSI in treatment of AAT compared to conventional systematic treatment. A total of 53 patients were enrolled, all of them diagnosed with delayed treatment of NIHL and were randomized into a transtympanic group (TR group, n = 27) and a control group (n = 26).

Exclusion criteria were history of any kind of otological disease treated or untreated, as well as hearing recovery of 15>= dB HL (average among 2, 4, 6 kHz) within the first 3 days of onset.

The control group received only conventional steroid treatment consisting of the a protocol outlined by Fisch in 1983: MP (125 mg i.v. for the 1st day, followed by 32 mg per day p.o. for 5 days, 16 mg per day for 2 days and 8 mg per day for another 2 days), naftidrofuryl (200 mg p.o.), diazepam (5 mg p.os) and low-molecular-weight heparin (0.4 ml) or low-molecular-weight dextran

(500 ml i.v.).
The TR group received the conventional steroid treatment plus 4 courses of additional transtympanic injections of MP 3 days after NIHL onset. Transtympanic injection was performed through laser-assisted myringotomy (a 0.5- to 1-mm perforation in the tympanic membrane) under microscopic vision.

Pure tone audiometry (PTA) and Speech Discrimination Score (SDS) were performed in both groups, 8 weeks after the onset.

A total of 51.9% of the patients in the TR group (S+ITSI) improved hearing levels by >15 dB in average, compared with only 23.1% of the controls, at the 8-week follow-up PTA.
A total of 66.7% of patients in the TR group had an improvement of >15% in the speech discrimination score (SDS) compared with 30.8% of patients in the control group, in the same time frame. Differences between the 2 groups were statistically significant. Complications were rare and insignificant, including mild pain and temporary episodic vertigo. (45)

Psillas et al. (2008), performed a randomized study with a sample of 52 soldiers exposed in gunfire noise. Aim of this study was to evaluate early onset treatment of acute acoustic trauma with corticosteroids.

Patients were young (mean 22.87 yo) and all suffered by AAT caused by the same noise source (gunshot of G3 rifle).
They were sorted into 3 groups: Group A (n=20); treatment started within the 1st hour after the AAT, Group B (n=17); treatment onset between 1st and 16th hours after noise-exposure and Group C (n=15); treatment 24 h or more after the incident.

Treatment consisted of Prednisolone (PD) iv 75 mg/day; 3 x25mg and then tapered off for 10 days) and piracetam (8 mg /day for 10 days). PTA was performed at presentation, and on days 2, 7 and 30 after treatment initiation.

Statistical analysis using comparisons were made between the groups using Kruskal–Wallis, Mann–Whitney tests and Bonferroni correction.
In one month, 36 (69%) patients of all groups showed hearing improvement (complete or partial recovery) in PTA. Most patients with complete recovery after belonged in group A (65%) compared to group B(23.5%) and C (13.3%).

Moreover, in group A (treated within the 1st hour after AAT) , in the final audiogram, average

hearing threshold was statistically better ($P < 0.001$) than that of groups B and C. Finally, when audiometric measurements were compared in pairs for every time PTA was performed (days 1, 2, 7, 30), hearing level was significantly improved especially in high frequencies and after a week from the onset. (37)

Author, year	n.	Steroid	Admin. route	Time from onset	Dosage	Tests	Results	Ref.
Chang YS, 2018	19	PD DM	S (oral) + IT	3d-7d 7d<	PD: 60mg DM: 5mg/ml	PTA	Early treated improved compared to late treated	[38]
Choi N,2018	29	PD	S (oral)	1-16d (m. 9d)	60mg	PTA	Better outcome for prolonged therapy: 14d (10+4 tapering) vs 10d (5+5)	[28]
Yehudai N,2017	56	PD	S (oral)	<10 d	1mg/kg/d max 60mg	PTA	Treated compared to untreated. Possible benefit of early treatment	[39]
Chang YS, 2017	19	PD DM	S (oral) or IT+S	3d-14d	PD: 60mg DM: 5mg/ml	PTA	Combination benefit	[44]
Zhou Y,2013	53	MP	S (iv+oral) or IT+S	3d	1day: iv 125mg, tapering p.os	PTA, SDS	Combination (IT+S) better than S alone (in PTA and SDS)	[45]
Psillas,2008	52	PD	S (iv)	1hour 1-16h 24h<	iv:75mg (25mg x3) p.os:32mgtapering	PTA	Early treatment (within 1 h) improves recovery	[37]

Πίνακας 2 Clinical Studies including acute noise-induced hearing damage and steroid treatment

PD prednisolone; DM dexamethasone; MP methylprednisolone S systematic; IT intratympanic; iv intravenous; p.os oral; PTA pure tone audiometry; SDS speech discrimination score

DISCUSSION

"Rapid recovery from acoustic trauma: chicken soup, potato knish, or drug interaction?"
With this rather provocative title, *Cacace et al*. published in 2003 a case report of a patient who presented with acoustic trauma. Medical treatment with corticosteriods and a diuretic alone supposedely failed to irestore auditory function and his related symptoms (tinnitus and aural fullness) for a 2-week period. Rapid recovery of auditory function (dramatic improvement in pure tone thresholds; reappearance of DPOAEs) and abatement of related symptoms directly followed physiologic reactions from ingesting a food substance; potato knish. (26)
Despite the possible spontaneous recovery and the weak evidence presented in this study, it somehow comprehensively describes the treatment options in AAT today: watchful waiting, steroids and other experimental regimens.
There are no definitive Guidelines about therapeutic interventions in acute acoustic trauma. Subsequently, there are not any firm recommendations concerning the administration of glucocorticosteroids for ANIHL treatment, although these regimens have already been used for decates.
Meta-analyses on this clinical entity are not available yet.

Out of the studies presented arise many questions that ought to be answered in order to conclude the optimal therapeutic modalities by steroid administration for AAT.

Synthesis

Efficacy of steroids in ATT treatment
(do they really work?)

The initial question of this review is whether steroids treat AAT.
In all of the six clinical studies reviewed, there was a hearing threshold recovery at least for part of the population studied. Since it is well-known that spontaneous recovery in AAT is not uncommon, only indirectly, could the beneficial role of steroids be concluded, by the fact that higher doses and earlier onset of therapy were otoprotective; In other words, these observations would be rather

improbable if steroids did not have any effect on AAT.

In only one of the articles, in *Yahudai et al*. study there was a control group. All other articles enrolled patients who all received steroid therapy, despite differences in treatment duration, administration route and time of therapy onset. Since, there is evidence advocating the beneficial role of steroids, it might be considered unethical by many researchers to leave patients suffering from AAT untreated. This is a significant obstacle in conducting double blind randomized studies which would help clarifying the real benefit of corticosteroids. *Yahudai et al.* enrolled 186 soldiers complaining for audiological problems, of which 92 where confirmed with AAT and 56 of them presented for follow up. At the initial examination, military doctors decided whether a patient would receive treatment or not. There were no strict criteria for this selection, thus leading to an obvious selection bias. Since there was not a study protocol and there were no guidelines available the decision of whether to provide therapy to a soldier or not, was held by each doctor. So, possibly soldiers with worst PTA were more likely to receive steroid treatment. The absence of placebo-controled group may have confounded the outcome. Moreover, the 2 groups in comparison differed in initial HL thresholds in PTA.

Preclinical studies do not share the same ethical consideration about having an untreated control group, therefore they are quite useful in answering the initial question. These studies tested their results with control groups. Out of 9 articles included, 5 showed benefit of steroid administration measured by audiological tests. In 4 of them [(46), (48), (51), (54)] in all tests used (ABR, DPOAE), while in one (49) there was improvement in ABR thresholds but not in DPOAE. In 2 studies [(47), (52)] there was not a statistically significant audiological gain. Finally in 2 studies [(50), (53)] there were initially significantly better audiological measurements right after the noise incidence comparing to the control group, but 2 weeks after there was no difference detected.

This may reflect an early positive intervention of steroids in metabolic mechanisms affected by the noise injury, averting the TTS observed in untreated animals. Other recent studies in bibliography showed IHC – synaptic ribbon disconnection in mice subjected to intense noise which only induced TTS. (31) While ABR thresholds recovered, histological examination revealed hair loss (especially OHC). (32) This pathological findings may signal an early response to noise and an additional factor to future hearing loss, while not eliminating the known importance of HC loss in PTS and hearing loss. (33) This pathophysiology may be closely connected to cochlear synaptopathy, promising to offer answers and shed light on hidden hearing loss, a subject with increasing interest in audiology. (34)

Regimen selection
(which one?)

Over the last decades different types of steroids where administered in treating ANIHL. In the reviewed researches there were used the most frequently administered agents for the disease as seen in bibliography: Prednisolone (PD), Methylprednisolone (MP), and Dexamethasone (DM). In 5 out of the 6 clinical studies PD was chosen, in 2 DM and in 1 MP. Dexamethasone was used only in solution for intratympanic administartion. Prednisolone was the only oral agent selected by the researchers and only in 1 study it was also intravenously infused (37). *Zhou et al.* used methylprednisolone, both systematically and intratympanically.

Considering the preclinical studies, there were two steroids applied: Dexamethasone and methylprednisolone. Both of them in systematic and topical administration. There is a trend in favor of DM the last decade, with no clear explanation.
The various steroids used have not been compared when similarly administered in the reviewed studies and to the best of our knowledge in bibliography for AAT and HL in general.

Glucocorticoids are strikingly similar in their molecular structures. Their clinical effects are generally similar and so are their side effect profiles. Among the three agents, DM has no mineral-corticoid action in comparison with MP (0.5 potency relative to hydrocortisone; PRHC) and PD (0.8 PRHC). DM shows stronger anti-inflammatory efficacy (30 PRHC), compared to MP (5) and PD (4). DM also has a longer duration (Half-life 36-54 hours , versus 12-36 h for both PD and MP)
Because of these differences, equipotent doses are interchangeable provided. There are some studies comparing different steroid agents for other diseases, especially asthma (35) (36), but they did not conclude a certain clinical superiority of one agent over the other.

Dosage
(how much, how long?)

Generally, there were no major differences, considering dose and duration of therapy. Gold standard for oral PD was 60mg daily. This was the standard dose for 3 out of 4 studies, while in *Yahudai et al.* the protocol was 1mg/kg/d with a maximum of 60mg. Considering though that the population consisted of soldiers, young men, we could safely assume that the vast majority of the patients received a 60mg/d dose too.
PD was intravenously (iv) infused in a scheme of 75mg, divided into 3 doses for 1 day. In this study (37) PD intake continued per os tappering, with no more information about the exact daily

dosage.
MP in *Zhou et al*. article was administered following a *Fischer et al.* suggestion : 1 single iv dose of 125 mg, followed by oral tappering beginning with 32 mg. DM was used in ITSI in a 5mg/ml concentration.

The duration of therapy slightly varied between studies. *Yahudai et al.* did not follow a standard protocol since this was a retrospective study : treated soldier- patients received therapy from 7 to 10 days, with a mean of 7.8 days.
In 2 studies the total duration, including tapering was 10 days and in other 2, performed by the same research group 14 (10 + 4 days tappering).
There was a single study evaluating duration as a possible independent factor in the success of steroid AAT treatment. *Choi et al.* divided the patients into two groups and treated the 1st group for 14 days with oral PD (10 + 4 days tapering) and the 2nd group for a total of 10 days (5 full dose, tapering off for the remainder). (28)
Their results supported the clinical significance of high-dose PD for the prolonged therapy of 14 days.
In this study the population treated was homogenous; All patients were of the same gender (male) and of similar age and none of them had reported any previous otological history. The study though had several limitations. 1st, sample size in both groups was small. Second, there may have been some selection bias, because of the choice of the dosage. Since the study was not randomized, doctors might have chosen the higher-dose prolonged therapy for the patients with greater hearing loss. (28)

Treatment onset
(when?)

Another crucial question concerning AAT treatment is whether therapy onset consists a significact prognostic factor, considering patients affected by AAT. These patients are usually military personnel or civilians exposed to an intense noise, such as an explosion. In real life situations this means possible delay in approaching medical treatment and also possible co-existing injuries, even life-treatening, that could postpone therapy even more.
3 of the studies evaluated the time interval between steroid therapy initiation and the noise exposure incident.
In *Psillas et al.* study most of the patients (69%) showed a hearing improvement. Groups A, B and C, consisted of patients treated respectively within 1 hour, between 1-16 h and after 24 h or more. Group A patients had a better outcome in hearing recovery when compared to groups B and C,

showing thus benefit of the earliest onset of treatment; within the 1st hour after noise exposure. On the contrary, the outcome was quiet poor (53.3%) when treatment initiated 24 hours or more after exposure. (37)

In follow-up, hearing significantly ($P < 0.001$) improved in all frequencies for all 3 groups. In group A though, in the final audiogram, the average hearing threshold was higher comparing with the other two. Overall recovery in A Group conversely to B&C (90% of cases vs. 46–64%), supported the importance of treatment within the 1st hour.

Lack of control group makes difficult to establish what part of the post AAT hearing impairment can be attributed to spontaneous recovery. Besides, initial audiograms of the three groups differed, with group A having relatively better hearing in initial presentation, though this cannot be evaluated, since they were not compared. However, in this study the population was homogenous (young male soldiers) and even more important, it is maybe the only clinical study in which we may safely assume that the intense of the noise was of the same level. All patients were soldiers exposed to the sound of G3 rifle during gunshot training. G3 rifle produces an impulse with a peak at 161 dB (*Price G, Weapon Noise Exposure of the Human Ear Analyzed with the AHAAH Model, U.S. Army Research Laboratory*). This impulse noise was produced few centimeters of the subject's ear.

In *Chang et al.* 2018 study there was also evaluation of steroid therapy depending on the time of therapy onset; Group A started steroid intake between days 3 and 7 from the AAT, while Group B, 7 days or more after it. The results advocated a clear benefit of earlier onset.

However there were limitations. 1.Sample size was small, due to strict application of inclusion criteria to minimize the confounding factors. 2.There may have been some selection bias, as some patients refused ITSI treatment, thinking that it may be invasive with potential for numerous complications. This might have been more plausible among those with better hearing thresholds (indicating less severe AAT) during their initial examination. Their absence in this study may have skewed the results. 3.Although none of the enrolled subjects reported a history of hearing impairment from the hearing test conducted upon their conscription, these test results were not assessed and researchers had to judge their previous state from the subjects' recollections. Therefore, possibility of enrolling some subjects with some degree of hearing impairment could not be excluded. 4.Air-conduction threshold was the sole outcome parameter. Audiological examination may not be considered complete in this study, although in most of the reviewed articles there was not a complete audiological examination of the subjects. (38)

Yahudai et al. also supported a benefit of early onset of steroid therapy, but this may only indirectly be considered. This was a retrospective study; beside other correlations, there was a comparison of 2 groups considering intial treatment. With a rather broad definition, AAT was characterized "immediate" when patients presented up to 10 days from exposure and late when they presented later than 10 days. When soldiers presented ''immediately'' after the event, they were either

provided with oral steroid therapy or they are advised only be observed. As mentioned in the materials and methods section, the decision was based on the "otolaryngologist's experience". (39) When they presented 10 days or more after the incident, soldiers were not administered steroids. Subsequently, there was no internal distinction in "immediate" group in treated and untreated patients; this testing that might have established a superiority of earlier over later onset therapy.

Preclinical evidence supports to a certain point the beneficial role of early onset steroid treatment. *Tabuchi et al.*, found that when MP was administered immediately before or immediately after the termination of noise over-exposure it significantly improved ABR threshold shifts. When administered 3 hours or later it failed to show any hearing gain. This result seems consistant with the clinical findings of *Psillas et al.*, both suggesting that immediate in the field of treating AAT means hours and not days and that the treatment should probably be available within the first 1-3 hours. However a limitation of this experimental study was that only one protocol for inducing acoustic trauma (4-kHz pure tone at 128dB SPL for 4h) was tested. Pure tones at 4-kHz frequency of equal to or less than 120dB SPL did not provoke OHC loss but the data were not shown; also different intensity or duration noise may induce different pathological and subsequently audiological results.
Several older experimental studies in literature evidence how critical early onset treatment of AAT in the outcome of hearing loss is, especially for the first hour after exposure. (40) (41) (42)

Administration route
(IT or S?)

Currently, two main routes of steroid administration for otological disease are applied: systematic and intratympanic. Systematic administration may further be categorized in oral and intravenous.

Glucocorticoids in inner ear disorders, including hearing loss and ATT have a long history of use and were typically administered systematically.
Unfortunately, systematic intake of corticosteroids is associated with side effects, some of which are serious, including gastritis, hypertension, flashing, hyperglycemia, insulin resistance, episodic psychosis and aseptic necrosis of the hip. Cost may also be considered for intravenous systemic administration, since it requires hospitalization.

Transtympanic steroid administration (or intratympanic steroid injection - ITSI) was developed a few years ago.
The first clinical entity treated with ITSI was idiopathic sudden sensorineural hearing loss with

relatively promising results. (24) This method results in a higher concentration of the drug in the cochlea and the perilymph with lower levels in serum, than systematic steroid therapy (both p.os and IV). The possible explanation of that is the existence of a blood-labyrinth barrier. In animal experiments drug level concentration in the perilymph was double in intratympanic than in intravenous treatment. (43)

ITSI is not free of complications, although generally quite infrequent and insignificant. Long-term complications are almost absent in ITSI treated. The most frequent side effects are pain, transient vertigo after drug administration (may be prevented with heated agent in 37 °C), perforation of the eardrum and infection. ITSI also requires several times (2-4) presentation of the patient in the outpatient, while oral administration does not.

Among the studies there was not a direct comparison of different systemic ways of agent delivery, oral and intravenous, while in the bibliography they are generally considered equivalent. Intravenous administration tends to be abandoned in favor of oral and the recently rising ITSI.

There is also no clinical comparison of systematic (S) versus IT delivery. Two of the studies compared systematic with combined S and IT delivery of steroids.

Zhou et al. treated delayed ATT with MP concurently applied systematically (IV and orally) and localy (ITSI). In PTA test, combined therapy improved 51.9% of the patients thresholds (>15 dB), comparing to control group (23.1%). More interestingly there was improvement in Speech Discrimination Score test (SDS); significantly better in the S+IT group: 66.7% of the patients improved (>15%), in comparison with 30.8% in the conventional S treatment group. This study was randomized adding to the credibility of its results. Moreover this is the only clinical study where SDS was evaluated. Speech discrimination is of great importance, especially considering the latest research on hidden hearing loss, cochlear synaptopathy and the potential latent hearing failure in subjects who were exposed in loud noise and AT in young age. (33)

Zhou et al. results are promising for delayed AAT treatment, though when interpreting the study's conclusion we should consider the following: There are large variabilities in the source of the noise (military, concerts etc), in the extent of hearing loss and in the time interval between exposure and therapy. Moreover, some of the patients treated had already received some pharmaceutical therapy and some not. This might have obscured the results, since there is a possibility -even probably small- that the prior intake of another drug contributed in the threshold improvement. Finally, the sample size in this trial too, like in most, was small .

Chang et al. concluded a better outcome of concurrent S and IT steroid delivery over the conventional S. Combination of oral PD with IT DM showed an additional hearing improvement by 11.48 dB and in all frequencies affected (2 to 8 kHz).

The limitations of this study were the difficulty in follow-up, since the enrolled patients were soldiers, the small sample size, the fact that the S-only group had a slightly greater delay in

trherapy initiation. As already mentioned, there are studies in this review advocating the importance of early onset of therapy, so it is not clear if the benefit should be awarded to the administration route or the early onset. (44)

Apart from the clinical research there are experimental studies on applying steroids either systematically or locally. *Zhou et al.*, before performing the clinical research mentioned, had already in 2009 published a laboratory test to evaluate the IT versus S administration. For that he used 3 groups of mice: treated with intratympanic MP, intramuscular MP and a control group. Both groups of MP treated animals had better hearing levels in ABR compared to the control, but there was no significant difference between the routes of administration.

Han et al., on the other hand grouped animals administered with: 1. DM IT, 2. DM intraperitoneal (IP) and 3. saline solution (control). The two DM treated groups showed recovery in ABR but not in DPOAE comparing to the control, whereas in this study too, there were no significant differences between them.

We must note that the systematic administration route used in these two studies (IM, IP), is not applied in human patients due to technical difficulties, although we may safely assume that they would not differ with other systematic steroid deliveries (IV, oral).

In order to maximize effect of steroids, *Mamelle et al*. in 2018 administered intratympanicaly DM with hyalouronic acid (HA) gel . DM was either free in the gel or loaded in liposomes. The agent failed to promote additional or faster hearing recovery ,compared with controls.

Additionally to the studies included in this review, it is worth commenting one that was excluded when assessed for eligibility. *Wada et al.* published in 2017 a study (27) with aim to evaluate the differences between AT and the other types of acute noise induced hearing loss (ANIHL) in treatment and prognosis. A literature review of 10 clinical studies on ANIHL and steroid treatment, published between 1984 and 2015 was presented on a chart, but without thoroughly commenting the results in the main body of the text, nor performing a statistical analysis of the data. Own cases were also presented. The article was excluded by the present review because it did not provide details of treatment or outcome (the regimens and dosage varied and the duration of therapy was unknown).

It suggested though an interesting concept: a distinction between AT and ANIHL. HL caused by gunshots and explosions was categorized into the AT group, while all other causes, such as recreational noise and noise in concerts into the ANIHL. After a statistical analysis, the conclusion was that hearing recovery after AT is very poor, if any, while hearing loss after ANIHL may partialy recover. This study has some significant limitations: it was neither prospective nor randomized, categorization was problematic, since real noise level was unkown and the sample

was very small (n=18).

Moreover, to the best of our knowledge, there is not a universally accepted definition of acoustic trauma or an acknowledgment of AT as a distinct entity from ANIHL. According to one offered definition in bibliography, acute acoustic trauma is caused by exposure to an intense noise, whose level exceeds the 'elastic limit' of the peripheral auditory mechanism. (28) It has been established already though, that the risk on hearing and structural damage of the inner ear depends both on the intensity and duration of the noise. (29)

Erdreich J suggested a definition of impulsive noise independent of specific characteristics such as duration and amplitude. In his paper published in 1986, he proposed an alternative to duration independence, a fixed time window over which a statistic is calculated. This was not widely accepted, so there is not a concensus in bibliography. (30) It is yet to be determined whether there is a critical point in noise intensity, after which cochlea is damaged so much, that hearing cannot recover by any treatment.

Limitations in AAT studies

There are a few points that ought to be stressed, concerning the difficulties and limitations of studies on AAT.

First, since there is growing evidence for the beneficial role of steroids in AAT treatment it might be considered unethical to plan a study which would contain a control group. Testing the efficacy of a regiment requires a sample group of patients that would intake a placebo, thus they would not be provided with the best potential therapy at the moment. Only retrospective studies may be performed so, enrolling patients who for several reasons were not treated.

Second, although AAT is relatively frequent, most studies had a small sample size. The reasons are not clear; they may involve spontaneous recovery and inconsistency in follow up, co-existing injuries of patients after a blast or military operations and more.

Third, in clinical studies, in contrast with preclinical, noise level is impossible to be measured at the time of the exposure. Extensive noise is produced by different sources, with different characteristics and at a different distance from the injured ear.

Limitations of animal studies

Appart from the already mentioned limitations, there are some additional considerations about preclinical studies. Although there are great similarities between the human and some animals auditory system, there is not an animal with an identical ear with human's. Sensitivity in noise is different and it is correlated to frequency. Moreover, although it is important that contrast to

clinical trials on NIHL noise in laboratory studies may be controlled, regulated and measured, it is arguable that a noise of specific characteristics would have the same impact in the human ear. Outcomes of the tests should be cautiously interpreted, since for example a hearing gain of 10 dB that might be considered efficacy in animal models is nearly noticable by a human. Finally, obviously animals cannot be tested for speech recognition and discrimination, abilities of great importance especially for patients with hearing loss.

CONCLUSIONS

Steroids remain the sole pharmacological therapeutic option for acute noise-induced hearing loss today.

In this review we have tried to answer a number of questions in order to suggest the optimum possible treatment for AAT, regarding the efficacy, the regimen type, the dosage, the duration, the onset and the administration route of steroid therapy.

After thouroughly studying recent literature on acoustic trauma, we may conclude the following:

- Steroids offer a reliable treatment for patients with AAT. All clinical and most experimental studies in this review present a benefit on hearing recovery from corticosteroid administration. However, the lack of control groups in clinical research trivials the results of the regimens' application; the exact amount of hearing gain and the beneficial function of the agent beyond spontaneous recovery. The positive outcomes of steroid therapy are yet to be quantitatively determined. Concerning experimental studies, in 7 out of 9, steroid efficacy was audiologically confirmed. In 2 of them though, treated groups showed better recovery only in the initial tests. This may imply synaptopathy and hidden hearing loss mechanisms of AT.

- There is no study comparing different steroid agents, when similarly administered. There is no evidence of superiority of one agent to the other. Generally, prednisolone is prefered in systemic (oral) administation, while dexamethasone in intratympanic.

- There is no research comparing daily dose effectiveness of the same regimen. There is 1 clinical study in which overal higher dosage, by virtue of of prolonged therapy is found to be superior. Total 14 days oral PD (10+4 d tapering) had better results from 10 days (5+5 d tapering).

- Early onset of therapy is important in the final outcome. 2 clinical studies directly compared earlier to later initiation of treatment and found early onset superiority. Experimental evidence on animals from one research confirms the above. Steroid administration within the first hour after the noise exposure is the optimum.

- Concurrent systematic (S) and intratympanic (ITSI) administration offers possibly the best outcome for hearing recovery after AAT. There is no direct clinical contrast of S to solely IT intake but the comparison between S and IT+S in 2 studies revealed superiority of the combination in audiological

measurements and final outcome. In experimental enviroment 2 articles compared S to IT to control. Steroids offered better results in hearing recovery in contrast with the control, but there was not significant difference between the two routes of administration. There was not a test of the combination in the laboratory. One of the interesting findings though, is that the route of steroid administration offers otoprotection with a different pathophysiological mechanism. Systemic intake maintains the integrity of the organ of Corti, while intratympanic reduces OHC loss. Thus, we may conclude a possible maximum otoprotection by the concurent IT + S administration.

Considering the lack of definitive Guidelines, as well as meta-analyses on AAT treatment, more research is needed to optimize the steroid or other offered therapies. Randomized and prespective clinical studies with larger sample sizes and strict eligibility criteria are required.

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