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Article

Preservation of hearing in partial deafness patients who received two different regimes of corticosteroid therapy following cochlear implantation: one-year observations

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The objective of this study was to assess how different modes of steroid therapy affect hearing preservation in Partial Deafness Treatment group of patients. In this study, the group consisted of 46 (24 women, 22 men; aged 18–78 years) cochlear implant patients divided into 3 subgroups. In the first subgroup (N = 13), patients underwent standard intravenous (IV) steroid therapy following implantation. In the second (N = 16), patients underwent prolonged treatment with a combination of oral and IV corticosteroids. Third subgroup (N = 17) was a control group who received no steroids therapy. The mean hearing preservation rate was 52.1% (SD = 36.7) in patients receiving standard steroid therapy, 71.4% (SD = 22.7) in patients with prolonged steroid therapy, and 22.1% (SD = 33.9) in control patients. The smallest variation of hearing preservation rate was observed in patients with prolonged steroid therapy and was 9.9 dB. In comparison, the mean change in patients with standard steroid therapy was 11.7 dB and for control patients the figure was 18.0 dB. A combination of intravenous and oral steroid therapy seems to be optimal and stabilizes hearing thresholds and preserves hearing.

Keywords: Off-label use. Intensive Care Units. Critical Care. High-alert medication.

INTRODUCTION

Cochlear implantation is now considered the "gold standard" as a treatment for hearing impairment (Brown *et al.*, 1995; Teschner *et al.*, 2013). Irrespective of the implantation technique used, leading otorhinolaryngological centers are now looking closer at other (non-surgical) factors which can help improve rates of hearing preservation, particularly for those patients who are classed as suffering from partial deafness (Nguyen *et al.*, 2016; Rah *et al.*, 2016; Skarzynski *et al.*, 2010, 2012, 2016; Sweeney *et al.*, 2015; Van Abel *et al.*, 2015).

Cochlear implantation is a multidisciplinary therapy that is often a very good solution for children or adults afflicted with deafness (Dixon *et al.*, 2019; Sarant *et al.*, 2019; Skarzynski *et al.*, 2012). Indications for implantation are much broader than they were many years ago, a trend which reflects the significant benefits to be had in speech understanding. This means that patients with partial deafness, or even single-sided deafness, are also likely to benefit (Lorens *et al.*, 2019; Ramos Macías *et al.*, 2019; Skarzynski *et al.*, 2016, 2013).

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Cochlear implants (CIs) are designed for individuals with moderate to profound sensorineural hearing loss who are unable to gain much benefit from hearing aids and need a practical solution to their hearing loss. CIs bypass the non-functioning part of the auditory system to provide electrical signals directly to the auditory nerve. Studies have shown that cochlear implantation is a safe and effective procedure in both children and adults with prelingual or postlingual deafness.

There are many publications related to surgical technique. For example, some authors see benefits from the round window approach, while others favour the cochleostomy approach to scala tympani. Based on the majority of papers, the round window approach seems to offer better and less traumatic electrode insertion (Fontenot *et al.*, 2019; Sosna *et al.*, 2019; Stuermer *et al.*, 2019). In patients for whom hearing preservation is possible, the question needs to be raised: are there other factors other than surgical that can lead to better preservation of residual hearing? One particular unresolved matter is the means by which drugs are delivered to the cochlea or middle ear (Creber *et al.*, 2019; Murillo-Cuesta *et al.*, 2017; Pierstorff *et al.*, 2018). Systemic or local pharmacotherapy using glucocorticoids is widely used in otorhinolaryngological practice for severe or chronic diseases such as Meniere's disease, sudden sensorineural hearing loss, autoimmune disorders, or following a surgical procedure (Alles, der Gaag, Stokroos, 2006; Chrousos, 2007; Hamid, Trune, 2008). According to current knowledge, none of these pharmacological agents are authorized as a treatment for protecting or restoring hearing. The only treatment for profound hearing loss, as authorized by the U.S. Food and Drug Administration and its European counterparts, is cochlear implantation (Nyberg *et al.*, 2019).

Insertion of the frequency-specific electrode array into the cochlea is a delicate operation and requires a very careful surgical technique. Even with the utmost care, however, it is difficult not to cause some tissue damage, especially in cases of partial deafness where there are still some partially functioning hair cells. In this situation, use of corticosteroids (local or systemic) is important: these drugs can reduce oxidative stress, inflammatory reaction, and the apoptosis of hair cells due to insertion damage. A major challenge in effectively delivering pharmacological agents to the cochlea is its physical inaccessibility and the presence of a blood/labyrinth barrier. These factors are especially apt for patients suffering partial deafness, where the hair cells at the apex of the cochlea (responsible for receiving low frequencies) are anatomically remote.

Pharmacokinetics of drugs and delivery to the inner ear

From a pharmacokinetic point of view, the inner ear can be considered to be made up of multiple fluid compartments in hydrostatic balance (maintained by the blood/labyrinth barrier). The pharmacokinetic process is helpfully described by the acronym LADME (*L*, liberation; *A*, absorption; *D*, distribution; *M*, metabolism; *E*, elimination). The first step, liberation, means that the drug (or its carrier) must be water soluble, so that it can easily be carried in the blood. A key factor here is the protein binding of the drug: the greater the protein binding of the drug, the longer its therapeutic activity. The finite binding between the protein and the drug molecule allows the drug to gradually liberate (Nyberg *et al.*, 2019).

The next pharmacokinetic step is absorption, and this depends on lipophilicity and the solubility of the drug (Nyberg *et al.*, 2019). Only a few drugs can be used effectively in otorhinolaryngological practice due to the difficulty of achieving sufficient concentrations in the inner ear (Salt, Plontke, 2018). Two groups of drugs are commonly used in clinical practice: aminoglycosides (mainly gentamicin) in pharmacotherapy of Meniere's disease, and corticosteroids (dexamethasone, triamcinolone, and dexamethasone) in pharmacotherapy for idiopathic sudden sensorineural hearing lossand other cases of acute hearing loss (Hamid, Trune, 2008).

The distribution process depends on many different factors such as route of administration, mode of administration, single or repeated administration, dose, ionic composition, pH, and osmolarity. The elimination a drug from the body (its clearance rate) depends on the same set of chemical and physical properties.

No method of administering glucocorticoids in otorhinolaryngological practice is ideal. Local administration (e.g. transtympanic injection) allows one

to achieve a high concentration in the middle ear, but the presence of the Eustachian tube means the active ingredients may be lost. Some advantages of local delivery into the inner ear are that it avoids the "first pass" effect, reduces the required dose of the drug (and hence its adverse effects), and bypasses the blood/labyrinth barrier. It should be stressed that in this way the drug is used *off-label* – since no appropriate clinical trials have been carried out. An example is the use of dexamethasone phosphateintravenously delivered via transtympanic injection.

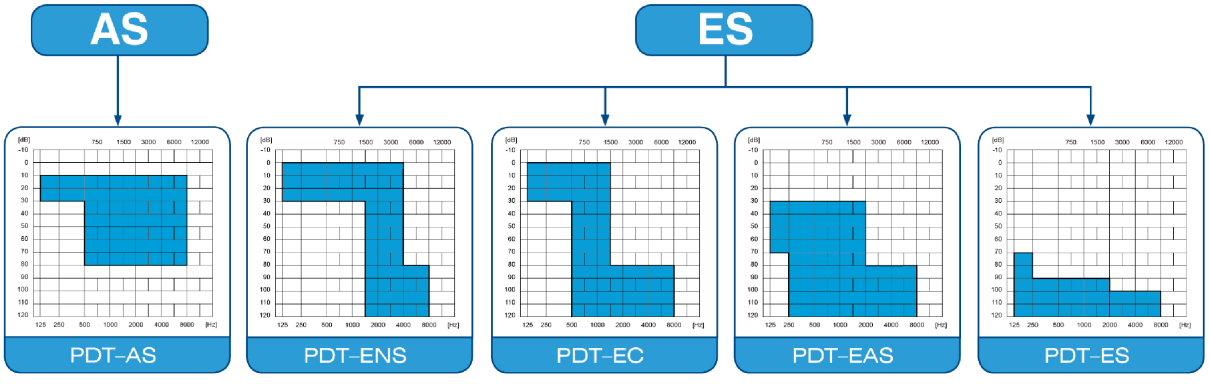
Local drug delivery may involve intracochlear administration (e.g. stem cell or gene therapy), extracochlear administration (e.g. intratympanic injection), or a combination of both. Systemic delivery is a non-invasive way of delivering medical substances to the inner ear via circulation of blood to the inner ear; there is also no damage to the tympanic membrane or other anatomical structures of the ear. However, the side effects of systemic delivery may lead to termination of the pharmacotherapy.

In a study published in 2017, Plontke, Götze, Rahne, &Liebau compared the effects of dexamethasone with saline (in a guinea pig model). Both substances were administrated intravenously 60 minutes before implantation. The conclusion was that dexamethasone could reduce scarring in the hook region or near the electrode tip, but they did not see any relation between dexamethasone and reduction of fibrosis relating to cochleostomy. At the same time, *in vitro* studies have shown a correlation between reduction (loss) of auditory cells after exposure to tumor necrosis factor alpha and dexamethasone-releasing polymer (used to coat the CI electrode carrier) (Plontke *et al.*, 2017).

MATERIAL AND METHODS

Scheme of corticosteroid administration

The main aim of the study was to compare the hearing preservation levels of partial deafness patients following cochlear implant surgery when two different procedures for administrating dexamethasone (or dexamethasone and prednisone) were used. The protocol of this prospective clinical trial was approved by the Bioethical Commission (consent number KB/06/2016). Patients enrolled in the study suffered severe to profound hearing loss and were classified according to the Skarżyński Partial Deafness Treatment (PDT) classification scheme(Skarzynski *et al.*, 2013)into two groups: PDT-EC (Partial Deafness Treatment – Electrical Stimulation)or PDT-EAS (Partial Deafness Treatment – Electro-Acoustic Stimulation) (Figure 1).



AS – Acoustic Atimulation
ES – Electrics Stimulation
(PDT) Partial Deafness Treatment:
EAS - Electro-Acoustic Stimulation
EC – Elecrtical Complement
ENS – Electro-Natural Stimulation

FIGURE 1 - Partial deafness treatment groups for cochlear implantation. ENS: electro-natural stimulation; EC: electrical complement; EAS: electrical-acoustic stimulation; ES: electrical stimulation.

Inclusion and exclusion criteria were in accordance with the consensus of the international HEARRINGgroup on hearing preservation in cochlear implantation. Study eligibility criteria were participants ≥18 years of age with a cochlear duct ≥27.1 mm (measured by computerised tomography), with:

1. hearing levels in the range of 10–120 dB HL at frequencies of 125–250 Hz;
2. hearing levels of 35–120 dB HL at frequencies of 500–1,000 Hz;
3. hearing levels of 75–120 dB HL at frequencies of 2,000–8,000 Hz (Skarżyńska *et al.*, 2018).

All hearing levels were measured in HL decibels.

Exclusion criteria included suffering from a severe disease for which steroid treatment could worsen the patient's condition or where there might be possible interactions between the patient's medications and steroids. Non-parametric tests were used due to differences in the number of participants between subgroups, the small number of participants in the study, and violation of normal distribution of pure tone audiometry results (Skarżyńska *et al.*, 2018).

Materials

The46 patients enrolled in this prospective study were divided into 3 subgroups. Patients from the first subgroup (N = 13)underwent intravenous (IV) steroid therapy (Figure 2). For patients in the first subgroup, dexamethasone was administrated intravenously (0.1 mg per kg of body mass) 30 minutes before the cochlear implant surgery. The same dose was administered every 12 hours for 3 consecutive days (6 doses). The dexamethasone used in this study was supplied in ampoules of a 2 mL solution (4 mg/mL). Before injection, the sterile contents of the ampoule were diluted with isotonic sodium chloride solution. To standardise corticosteroid delivery, the IVroute of administration was chosen.

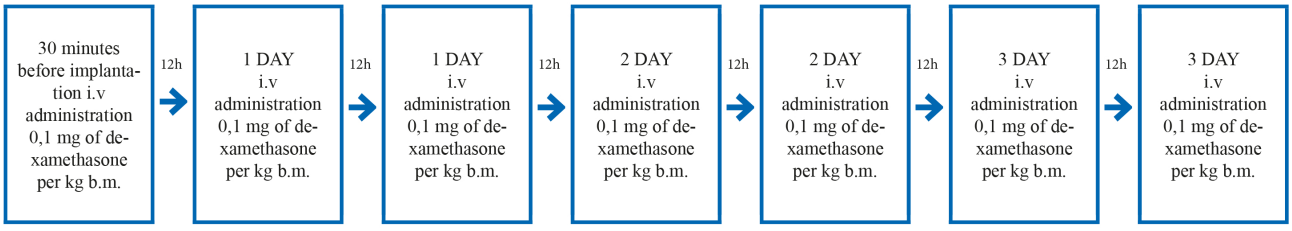


FIGURE 2 - Scheme of administration of corticosteroids in the first subgroup.

Patients from the second subgroup (N =16)underwent combined oral and IVcorticosteroid therapy (prolonged steroid therapy) following cochlear implantation (Figure 3). Prednisone was administrated orally at a dose of 1 mg per kg of body mass 3 days prior to surgery. Then 30 minutes before the implantation surgery, dexamethasone at a dose of 0.1 mg per kg body mass was administered IV(as with the first group). During the next 3 days, prednisone was administrated orally (1 mg of prednisone per kg body mass). After this time, the dose was reduced by about 10 mg per day until it reached zero. To investigate the effects of prolonged steroid administration, we chose to compare the IVand oral administration routes.

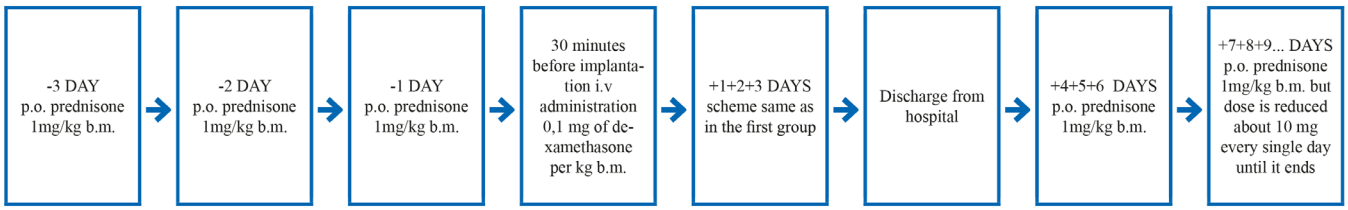


FIGURE 3 - Scheme of administration of corticosteroids in the second subgroup. The control subgroup of patients (N = 17) underwent a standard cochlear implantation procedure without steroid administration.

Characteristics of glucocorticoids

The adrenal cortex synthesizes two classes of steroids: corticosteroids (mineralocorticoids and glucocorticoids) and androgens. One of the differences between them is the number of carbon atoms: corticosteroids have 21 carbon atoms while androgens have 19. In the human body, the main glucocorticoid is cortisol and the main mineralocorticoid is aldosterone (Brunton, Knollman, Hilal-Dandan, 2017).

The glucocorticoid receptor is located in the cytoplasm and is inactive until it binds with the glucocorticoid molecule. This action results in the activation of the receptor and translocation complex (glucocorticoid–glucocorticoid receptor) to the nucleus. Activation of the receptor bases causes dissociation from the associated proteins. After translocation to the nucleus, the glucocorticoid–receptor complex interacts with specific, short DNA sequences in the regulatory regions. The regions are termed glucocorticoid-responsive elementsand allow induction of gene transcription by glucocorticoids. The process is complex because of interactions with specific cofactors and proteins, and is still not completely understood (Brunton, Knollman, Hilal-Dandan, 2017).

However, not only positive, but negative responses to glucocorticoid are possible. According to long-standing work, genes can also be negatively regulated by glucocorticoids (Webster, Cidlowski, 1999). The result of down-regulation (negative regulation) is to repress the expression of the genes responsible for encoding cytokines or enzymes (e.g. collagenase). Both play an important role in inflammatory and immune reactions. This negative expression appears to play a key function in anti-inflammatory and immunosuppressive effects of glucocorticoids (Barnes, 1998; Beato, Truss, Chávez, 1996; Smoak, Cidlowski, 2004). The anti-inflammatory activity of representative glucocorticoids is presented in Table I. Dexamethasone and betamethasone are two glucocorticoids with the highest anti-inflammatory activity. If cortisol has an anti-inflammatory activity of 1, then prednisone, prednisolone, triamcinolone, and 6α-methylprednisone are 4–5 times stronger, and have longer half-lives than cortisol. Half-lives of representative glucocorticoids are shown in Table I.

TABLE I - Characteristics of representative corticosteroids(Brunton, Knollman, Hilal-Dandan, 2017)

	Anti-inflammatory activity	Biological half-life, $t_{1/2}$
Cortisol	1	Short: $t_{1/2}$ = 8–12 h
Cortisone	0.8	Short: $t_{1/2}$ = 8–12 h
Fludrocortisone	10	Intermediate: $t_{1/2}$ = 12–36 h
Prednisone	4	Intermediate: $t_{1/2}$ = 12–36 h
Prednisolone	4	Intermediate: $t_{1/2}$ = 12–36 h
6α-methylprednisone	5	Intermediate: $t_{1/2}$ = 12–36 h
Triamcinolone	5	Intermediate: $t_{1/2}$ = 12–36 h
Betamethasone	25	Long: $t_{1/2}$ = 36–72 h
Dexamethasone	25	Long: $t_{1/2}$ = 36–72 h

Dexamethasone is a synthetic glucocorticosteroid (molecular weight 392 g/mol)with anti-inflammatory, anti-allergic, and immunomodulating activity. In common practice, dexamethasone is administrated IVor off-label as transtympanic injections. After intravenousadministration,the mean time to peak concentration is 10 to 30 minutes and the half-life is 2.2 to 3.8 h. Transport proteins are responsible for transport and distribution of dexamethasone in the blood. Specific blood transport proteins also determine transport of adrenal gland hormones from the adrenal cortex as well. Dexamethasone is mainly metabolized by the liver and eliminated in the bile; only 2.6 % of the initial dose is eliminated via the kidneys. In this study the sodium phosphate salt of dexamethasone was used.

Prednisone is a synthetic glucocorticosteroid (a derivative of cortisone) and classified according to the Anatomical Therapeutic Chemical Classification Systemas H02 AB 07. Prednisone is a prodrugwhich converts into the active metabolite, prednisolone,with a higher anti-inflammatory activity. The bioavailability of prednisone administrated orally is 70– 90%. The mean time to peak concentration is 1–2 h and the half-life in plasma is 3.4–3.8 h and in tissue 18–36 h. The binding of prednisone to plasma proteins is 70–73%, although the binding of the active metabolite (prednisolone) to plasma proteins is higher (90–95%). Similarly to dexamethasone, prednisone is metabolized mainly in the liver and eliminated in the bile. Data here is based on data sheets of the drugs used in this study.

Measures and statistical analysis

The primary outcome variables were mean hearing thresholds averaged across all 11 measured frequencies (0.125–8 kHz). A secondary outcome variable was hearing preservation. Hearing preservation (HP) was calculated by comparing hearing thresholds in the 1-year post-operative period with preoperative hearing thresholds according to the HP formula in section 3.3 and classified into one of three levels: minimal, partial, or complete hearing preservation.

The clinical effect of administered substances was evaluated by pure tone audiometry over six different periods: before cochlear implant surgery (*first point*), at activation of the audio processor (*second point*), and 1

(*third point)*, 6 (*fourth point*), 9 (*fifth point*),and 12 months (*sixth point*) after activation of the audio processor. Non-parametric tests were used due to the differences in size between each of the groups. Statistical analysis was performed using IBM SPSS software v.24.0.

Non-parametric tests were used due to the violation of normal distribution in the results of pure tone audiometry and the unequal number of patients in the three groups. A Kruskal–Wallis test (statistic denoted by *H*) was used to compare hearing thresholds obtained by the patients in each separate period. The analysis continued with pairwise comparisons (with Bonferroni correction). The Wilcoxon signed-rank test (test statistic denoted by *T*) was used for testing differences between hearing thresholds in the preoperative period and in the 12-month post-activation period. A chi-square test (test statistic denoted by χ^2) was used to assess the differences between the three groups of patients in terms of hearing preservation. Values of $p<0.05$ were considered statistically significant. For statistical analysis IBM SPSS Statistics v.24 was used.

Characteristics of participants

There were 46 patients (24 women, 22 men) aged 18–78 years (M = 49.4; SD = 16.5). There were no significant differences in age, sex, and hearing characteristics between the three groups of patients (Table II).

TABLE II - Demographics and preoperative hearing levels of the patients

	Intravenous (IV) group (N = 16)	Oral and IV group (N = 13)	Control group (N = 17)
Demographics			
Age (yr) [a,b]	26–68; 47.9 ±15.7	24–78; 54.0 ±17.6	18– 4; 47.4 ±16.8
Sex (M:F) (%) [a]	56:44	54:46	35:65
Hearing characteristics			
Laterality of operated ear (R:L) (%) [a]	50:50	46:54	65:35
Mean of frequencies	63.9–100.5 87.9 ±10.8	65.0–102.3 85.9 ±12.4	65.9–106.6 90.9 ±12.1

[a] There were no significant differences in baseline characteristics between the three groups of patients
[b] Continuous variables are expressed as range; mean ± standard deviation
M, male; F, female; R, right ear; L, left ear

RESULTS AND DISCUSSION

Differences in hearing thresholds between groups

The values of mean hearing thresholds for all patients, according to treatment type are set out in Table III.

TABLE III - Hearing thresholds of patients from the three groups at each time point

		Min	Max	M	SD	Q1	Me	Q3
Intravenous (IV) group	Preoperation	63.86	100.45	87.94	10.76	79.55	87.95	98.69
	Activation	71.82	109.09	99.12	10.84	93.07	103.86	107.16
	1 month follow-up	66.82	110.00	97.39	11.44	88.64	98.64	107.27
	6 months follow-up	64.55	109.09	95.97	12.03	87.95	98.86	104.89
	9 months follow-up	62.73	109.09	96.69	11.21	92.95	97.73	102.95
	1 year follow-up	59.50	112.78	96.94	13.17	92.50	97.72	105.00
Oral and IV group	Preoperation	65.00	102.27	85.91	12.37	76.59	80.00	97.84
	Activation	80.91	105.91	96.05	6.89	91.36	96.36	100.91
	1 month follow-up	75.45	104.09	93.64	7.93	89.09	92.73	101.14
	6 months follow-up	82.73	102.73	93.57	6.70	88.64	93.18	99.77
	9 months follow-up	80.45	103.64	94.55	7.56	87.05	96.82	101.14
	1 year follow-up	83.33	105.00	94.05	6.97	87.75	96.11	100.58
Control group	Preoperation	65.91	106.59	90.92	12.07	81.25	92.73	101.70
	Activation	89.55	110.00	105.05	6.25	99.55	108.64	110.00
	1 month follow-up	85.00	110.00	104.44	8.13	100.00	109.09	110.00
	6 months follow-up	86.36	110.00	106.19	6.45	103.30	110.00	110.00
	9 months follow-up	84.55	110.00	105.94	6.89	103.07	110.00	110.00
	1 year follow-up	78.33	112.78	106.09	8.01	104.32	110.00	110.00

Min, minimum; Max, maximum; M, mean; SD, standard deviation; Q1, lower quartile; Me, median; Q3, upper quartile
Unit of measurement – dB

Statistical analysis revealed that there were no significant differences between groups in the preoperative period: $H = 1.50$; $p = 0.472$.

In the activation period there were significant differences between groups: $H = 11.60$; $p = 0.003$. Patients receiving prolonged steroid therapy had significantly better mean hearing thresholds compared to control patients ($p = 0.002$).

Also, 1 month after activation there were significant differences between the groups: $H = 11.25$; $p = 0.003$. Patients receiving prolonged steroid therapy had significantly better mean hearing thresholds in comparison with control patients ($p = 0.002$).

At 6 months after activation there were significant differences between groups: $H = 16.32$; $p<0.001$. Again, patients with prolonged steroid therapy had significantly better mean hearing thresholds in comparison with control patients ($p<0.001$). Additionally, patients receiving standard steroid therapy had significantly better mean hearing thresholds than control patients ($p = 0.001$).

At 9 months after activation there were significant differences between groups: $H = 16.75$; $p<0.001$. The results were similar: significantly better mean hearing thresholds in patients with prolonged steroid therapy than in controls ($p<0.001$) and significantly better mean hearing thresholds in patients with standard steroid therapy than in controls ($p = 0.001$).

The pattern of results remained stable at 1-year post-activation: there were significant differences between groups, with $H = 14.49$; $p = 0.001$. Again, patients with prolonged steroid therapy had significantly better mean hearing thresholds than controls ($p<0.001$) and patients with standard steroid therapy had significantly better mean hearing thresholds than controls ($p = 0.014$).

There were no statistically significant differences in mean hearing thresholds between the two corticosteroid groups in any of the analysed periods.

Differences in hearing thresholds within groups

A deterioration in hearing thresholds was observed at the 12-month follow-up in comparison with the preoperative period in all three groups of patients, but the size of this change differed.

Patients with standard steroid therapy had better hearing thresholds in the preoperative period (M = 87.9; SD = 10.8) than after 12 months (M = 96.9; SD = 13.2); the difference was statistically significant: $T = 2.87$; $p = 0.004$).

Patients with prolonged steroid therapy had better hearing thresholds in the preoperative period (M = 85.9; SD = 12.4) than after 12 months (M = 94.1; SD = 7.0); the difference was statistically significant ($T = 2.13$; $p = 0.033$).

Control patients had better hearing thresholds in the preoperative period (M = 90.9; SD = 12.1) than after 12 months (M = 106.1; SD = 8.0); the difference was statistically significant ($T = 3.52$; $p<0.001$).

Although a deterioration of hearing thresholds was found in all three groups of patients, the mean change was the smallest in patients with prolonged steroid therapy: 9.9 dB. The mean change in patients with standard steroid therapy was 11.7 dB and the mean change in control patients was 18.0 dB.

The biggest deterioration of mean hearing thresholds for each frequency occurred in control patients, and the smallest deterioration in patients with prolonged steroid therapy, as shown in Figure 4.

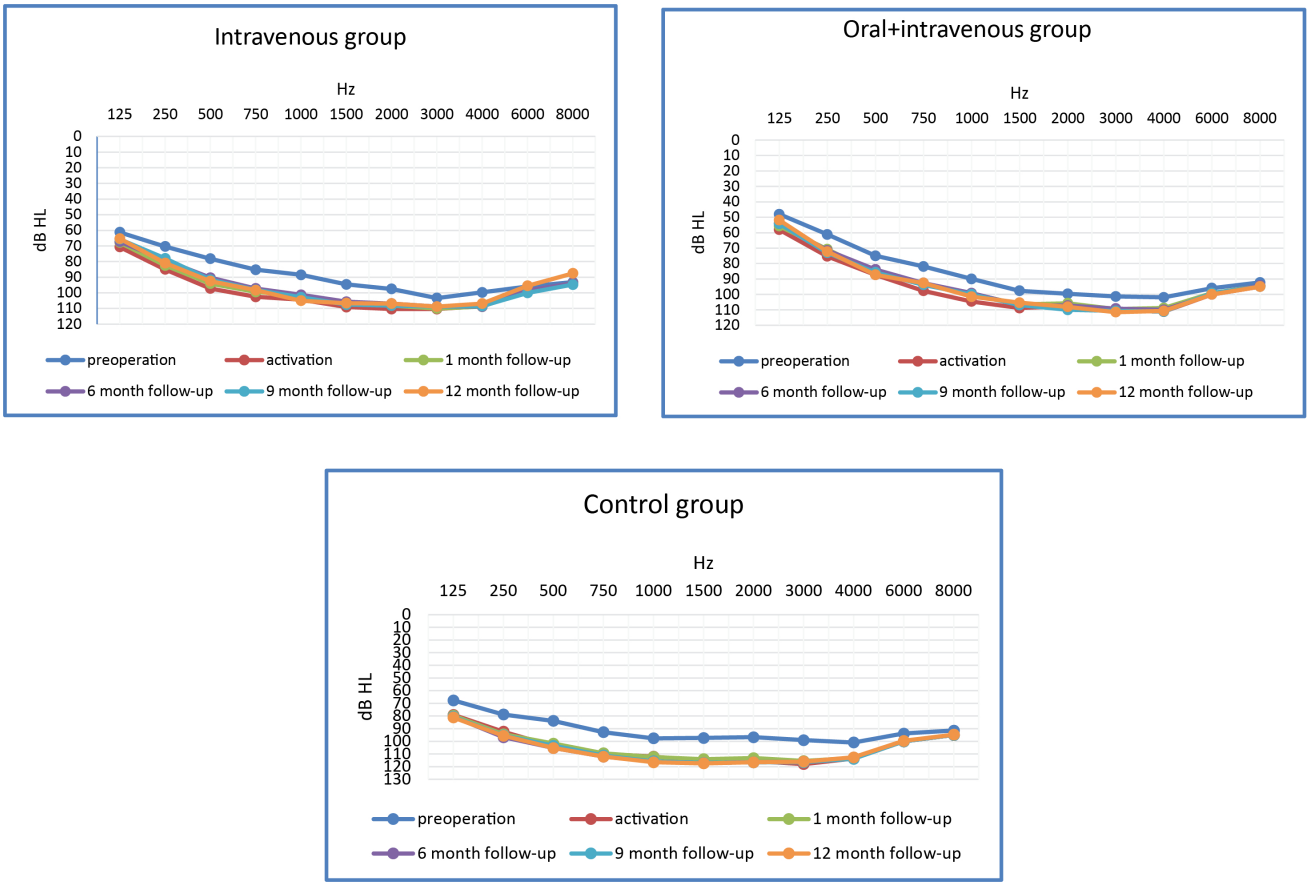


FIGURE 4 - Mean hearing thresholds of patients with standard steroid therapy (IV group), patients with prolonged steroid therapy (oral and IV group), and control patients at six time points: the pre-operative period, upon activation, and at 1, 6, 9, and 12 months.

Hearing preservation rate (*HP*)

The mean hearing preservation rate (*HP*) was 52.1% (SD = 36.7) in patients with standard steroid therapy, 71.4% (SD = 22.7) in patients with prolonged steroid therapy, and 22.1% (SD = 33.9) in control patients. The smallest variation in hearing preservation rate was observed in patients with prolonged steroid therapy.

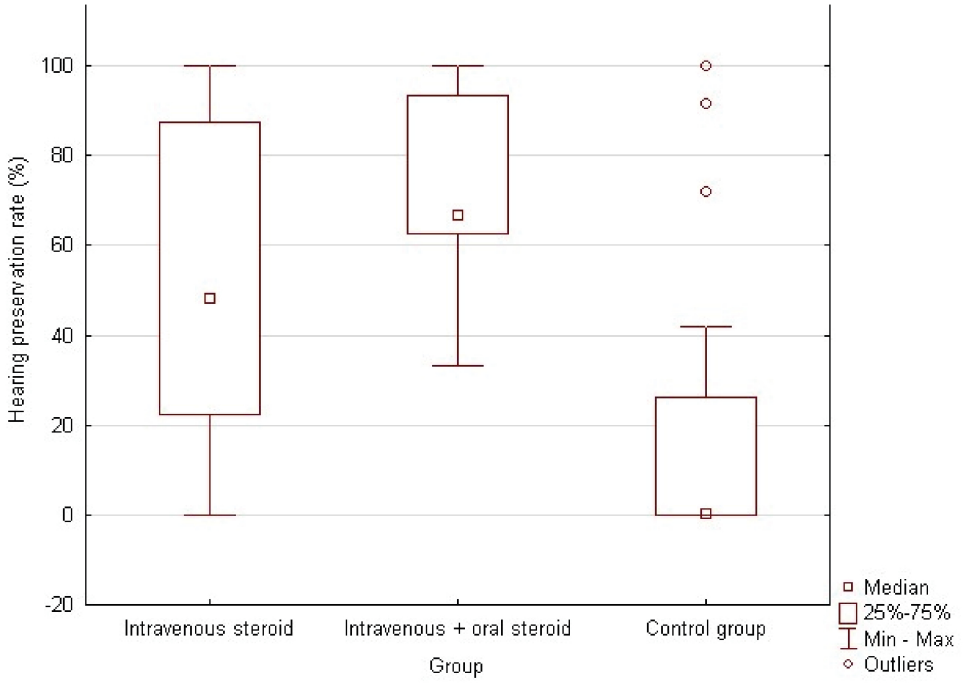
Data concerning hearing preservation, *HP*, converted to three categories (minimal, partial, complete), are set out in Table IV. *HP* is defined as follows:

In this equation, PTA_{pre} is the pure tone average measured preoperatively, PTA_{post} is the pure tone average measured postoperatively, and PTA_{max} is the maximum sound intensity generated by a standard audiometer (usually 120 dB HL) and *HP* is the degree of hearing preservation as a percentage (Skarżyński, Lorens, Skarżyński, 2014).

TABLE IV - Hearing preservation 12 months after CI implantation, according to type of treatment (Usami *et al*., 2011)

	Minimal	Partial	Complete
Intravenous group (IV)	5 (31.2)	7 (43.8)	4 (25.0)
Oral and IV group	0 (0.0)	8 (61.5)	5 (38.5)
Control group	12 (70.6)	3 (17.6)	2 (11.8)

Data are given as the number of patients (percentage in brackets)



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Oral and IV group	**0 (0.0)**	**8 (61.5)**	**5 (38.5)**
Control group	12 (70.6)	3 (17.6)	2 (11.8)

FIGURE 5 - Hearing preservation (HP) rate in the study groups.

There was a statistically significant relationship between treatment type and hearing preservation at 12 months after CI implantation: $\chi^2 = 16.12$; $p = 0.003$. All patients with prolonged steroid therapy, and nearly 69% of the patients with standard steroid therapy, had partial or complete hearing preservation, whereas the majority of control patients had minimal hearing preservation.

This study is a continuation of a previous study published 2 years ago (Skarżyńska *et al.*, 2018). The main aim of the present work was to observe patients over a longer time. The previous study had a fewer number of participants and shorter follow-up periods. As previously mentioned, the results of this study are similar to the previous one, but are more reliable. To our knowledge, this work is the first to report the findings of two different methods of steroid administration (standard and prolonged) in partial deafness patients who have undergone cochlear implantation. Our findings show that steroid therapy stabilizes hearing thresholds and preserves hearing ability in adult patients with partial deafness, with combined IVand oralsteroid therapy giving the best results.

The optimal route of administering drugs to the inner ear is still open. There are many obstacles in effectively transporting drugs to the inner ear, whether drug delivery is systemic or local. However, current knowledge of drug delivery to the inner ear is limited, although we do know that the blood/labyrinth barrier in the inner ear, which is responsible for separating the systemic from inner ear blood circulation, is comparable to the blood/brain barrier in restricting drug delivery (Nyberg *et al.*, 2019). The fluids of the inner ear maintain homeostasis via a variety of regulatory mechanisms involving blood supply and ion transport across the blood/labyrinth barrier(Salt, Plontke, 2018).

In the literature, only a few works dealing with administration of dexamethasone can be found. When comparing our results with related work, the difficulty is a lack of clear information about routes of administration, specific glucocorticoid used, duration of exposure, and concentration of glucocorticoid. A somewhat similar approach to administration of dexamethasone can be found in (Usami *et al.*, 2011). But this earlier study administered dexamethasone only once at a dose of 8 mg by accessing the cochlea via the niche of the round window.

Cho *et al.* (2016) analyzed the efficacy of preoperative and intraoperative steroid administration for preserving hearing after cochlear implantation. According to the study's protocol, they used dexamethasone at a dose of 5 mg/mL administered systemically before the operation and topically during surgery. In contrast to our study, where a wide range of audiometric frequencies was tested (125, 250, 500, 750, 1000, 1500, 2000, 3000, 4000, 6000, and 8000 Hz), Cho and colleagues calculated the pure tone average (PTA) from only four frequencies (250, 500, 1,000, and 2,000 Hz). Although the authors did not analyze the prolonged application of steroids, statistically significant differences were observed between the steroid group and the control group. This result suggests a beneficial effect from steroid treatment 1 year after surgery (Cho *et al.*, 2016). Our results are similar, based on a 12-month follow-up period and comparison with preoperative results.

In the 2017 study by Plontke, Götze, Rahne, &Liebau, the authors compared dexamethasone with saline. Both materials were administrated intravenously to guinea pigs 60 minutes before implantation. The authors concluded that dexamethasone could reduce scarring as the electrode negotiated the hook region or near the electrode tip, but they did not observe any relation between dexamethasone and reduction of fibrosis relating to cochleostomy. Another *in vitro* study showed a correlation between reduction (loss) of auditory cells after exposure to tumor necrosis factor alphaand dexamethasone-releasing polymer which was used to coat the CI electrode carrier (Plontke *et al.*, 2017).

In 2018, Lyu and colleagues used an animal model to look at the clinical effect of dexamethasone on endocochlear inflammation. Three administration routes were examined: transtympanically, peritoneally, and intracochlearly. The greatest reduction in fibrotic changes was observed using the intracochlear route. Transtympanic administration of dexamethasone did reduce inflammation, but to a lesser extent. Current methods do not allow histopathological examination of the living human cochlea (Lyu *et al.*, 2018).

Research using animal models has shown (Lyu *et al.*, 2018)that prolonged steroid therapy can significantly

improve hearing preservation (based on pharmacokinetic and morphological analysis) when the CI electrodes are covered with dexamethasone (specially formulated to have a controlled release). However, Honeder and colleagues (2016), in a guinea pig model, failed to confirm that steroids can have a positive effect on residual hearing. One reason for the different results may lie in the use of different steroids. In the first study, dexamethasone was employed, whereas the second used triamcinolone (Honeder *et al.*, 2016). Douchement and colleagues investigated the effects of steroids on a gerbil animal model. Animals were implanted with an electrode having, on one side of the animal, controlled release of dexamethasone (1% and 10% concentration) and, on the contralateral side, a conventional electrode. Hearing levels were established based on tone-burst auditory brainstem responses at 4–6 weeks post-implantation, and at one-year post-implantation for older gerbils. The one-year observations showed significantly improved hearing thresholds for the high frequencies, but the low frequency results were ambiguous (Douchement *et al.*, 2015).

The following study is a continuation of the project which was precisely described in the publication from 2018 (as a preliminary study), but with some differences. Firstly, the number of patients who were enrolled to the later study was bigger (46 comparing to 36 patients in the first one). Although the scheme of administration of glucocorticoids was identical in both studies, the results of frequency of Pure Tone Audiometry (PTA) was different. In the manuscript from 2018, the PTA frequency range was 125 – 8000 Hz, PTA was assessed in four periods: pre– implantation, during the processor activation, 1 month after the activation and 6 months after the activation, hearing preservation (HP) was observed in the perspective of 6 months. According to the methodology of the study described in the manuscript, PTA was estimated in six different periods (before the implantation, during the processor activation, 1, 6, 9 and 12 months after the activation) and the HP was observed in the perspective of 12 months. The results were confirmed.

The results of the analysis from both studies were similar and confirmed that in the second subgroup (combined oral and IV steroid) hearing remained stable during the follow –up periods and did not vary significantly. Based on the HP rate, in patients who received combined oral and IV steroids therapy, the smallest variability of results as well as the highest overall HP were observed (in both studies from 2018 and 2020). The conclusion is that the results of the publication from 2020 confirmed the results from 2018 providing longer observation period of the patients (6 months after the processor activation in comparison to 12 months period of observation). The results of the both studies showed that steroids therapy stabilizes hearing thresholds and preserves hearing ability in adult patients, and, with the combination of IV and oral steroid therapy, is an optimal treatment and administration regimen. To sum up, the results of the analysis in 6 months observation were confirmed in the study with one year observation, with the clear advantage of combined steroid regimen of administration. The results were proved not only in the study from 2018 but also in this analysis.

CONCLUSION

The results of this study have clearly shown the effect of steroids (dexamethasone and dexamethasone/prednisone) in stabilising mean hearing thresholds in both experimental subgroups in comparison with the control subgroup. In the preoperative period, the hearing thresholds of participants in all three subgroups were statistically indistinguishable. A deterioration in mean hearing thresholds was observed from the first point of measurement after cochlear implantation (point 2, activation point)until the last measurement point (point 6, 12-month follow-up). Although knowledge is limited, and many questions remain, our study contributes to discussions about the optimal way of administering steroids during the pre-, intra-, and postoperative period in partial deafness patients who are qualified for cochlear implantation.

Our data indicate that 100% of patients undergoing prolonged steroid therapy, and nearly 69% of patients undergoing standard steroid therapy, had partial or complete hearing preservation, whereas the majority of control patients (71%) had minimal hearing preservation.

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