Chapter

Role of Glucocorticoids in Hearing Preservation in Partial Deafness Treatment

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Abstract

During the last 15 years, cochlear implantation became available as a method of treatment for different types of hearing impairment. Leading, specialized centers have now introduced the analysis of the nonsurgical factors that could contribute to improve rates of hearing preservation in preoperative period, during surgery, or in postoperative period in patients who suffer from partial deafness. One of the approaches is using pharmacotherapy (glucocorticoids) as a factor that may improve hearing functions. Preservation of hearing in patients who suffered from partial deafness and underwent cochlear implantation by using two different regimes of corticosteroid therapy was the aim of the study carried out by the *World Hearing Center* (WHC). Forty-six patients were enrolled in the trial and divided into three subgroups. Hearing preservation (HP) was evaluated using pure tone audiometry (PTA) (11 frequencies ranging from 125 to 8000 Hz). The impact of administrated substances was evaluated by pure tone audiometry during six different periods: before cochlear implant surgery, during activation of audio processor, and 1, 6, 9, and 12 months after activation of audio processor in comparison with control group. According to *hearing preservation (HP)* classification, patients from the second group, to whom combined glucocorticoid therapy was administrated, achieved the best HP results. The complete hearing preservation index was observed in the highest percentage of patients from the second subgroup. The dispersion of measured values was lesser than in other subgroups. According to the results, administration of glucocorticoids (dexamethasone and prednisone or dexamethasone only) to the patients, who suffered from partial deafness and underwent cochlear implantation surgery, may be important in stabilization of hearing thresholds and in protection of hearing.

Keywords: glucocorticoids, dexamethasone, prednisone, partial deafness treatment, cochlear implant

1. Introduction

In the past cochlear implantation was a "gold standard" treatment method for patients who suffer from hearing impairment and dedicated only for patients totally deaf. During the last 15 years, cochlear implantation became available also as a treatment for different types of hearing impairment. Regardless of surgical technique for cochlear implantation (cochleostomy or an approach through the round window), specialized centers have now introduced the comprehensive analysis of

the nonsurgical factors that could contribute to improve rates of hearing preservation in preoperative, during surgery, or in postoperative period in patients who suffer from partial deafness. One of the approaches of many leading research centers is using pharmacotherapy (glucocorticoids) as a factor which may improve hearing functions following cochlear implantation [1, 2]. Glucocorticoids play an important role in pharmacotherapy of many different otorhinolaryngological diseases, such as Meniere's disease, sudden sensorineural hearing loss (SSNHL), and tinnitus, and as a part of otorhinolaryngological procedures in surgeries (e.g., cochlear implantation) [3, 4]. The effects of treatment listed diseases are different and mainly depend on treatment results, adverse effects of used medications, and additional pharmacological treatment that was used during treatment. Unfortunately, the side effects of glucocorticoids are serious, and as the result, sometimes pharmacotherapy has to be stopped, and discontinuation of therapy is the only solution.

On the one hand, insertion of specific electrode of cochlear implant requires perfection in surgical techniques, but on the other it is difficult to do perfectly. Clinically approved algorithm of corticosteroid therapy (local or systematic) is discussed as one factor in reducing oxidative stress, an inflammatory reaction, and as a result apoptosis of hearing cells. A major challenge in effective administration and delivery medicines is the *blood-labyrinth barrier* (BLB) and physical inaccessibility of the inner ear, especially the apical part of the cochlea. It seems to be crucial especially for patients who suffer from partial deafness (PD) (apical hair cells are responsible for receiving low frequencies).

1.1 Characteristic: glucocorticoids

The adrenal cortex synthesizes two classes of steroids: corticosteroids (mineralocorticoids and glucocorticoids) and androgens. One of the differences is the number of carbon atoms. Corticosteroids have 21 carbon atoms, and androgens have 19 carbon atoms. In the human body, the main glucocorticoid is cortisol, and the main mineralocorticoid is aldosterone [5].

Glucocorticoid receptor (GR) is located in the cytoplasm in inactive form until it binds with the molecule of glucocorticoid. This action results in activation of receptor and translocation complex: *glucocorticoid receptor for glucocorticoid* to the nucleus. Activation of receptor is based on dissociation from the associated proteins. After translocation to the nucleus, a complex of glucocorticoid receptor interacts with specific, short DNA sequences with the regulatory regions. The regions are termed *glucocorticoid responsive elements* (GREs) and allow induction of the gene transcription by glucocorticoids. This process is very complicated because of interaction with specific cofactors and proteins and still not well and completely understood by scientists and researchers [5]. Not only positive response to glucocorticoid is possible. According to Webster and Cidlowski, genes negatively regulated by glucocorticoids were also identified [6]. An example of downregulation (negative regulation) is to repress the expression of gene responsible for encoding cytokines or enzymes (e.g., collagenase). Both play an important role in inflammatory and immune reactions. According to the information provided, this negative expression appears to play a key function in anti-inflammatory and immunosuppressive effects of the glucocorticoids. Anti-inflammatory activity of representative glucocorticoids is presented below (**Table 1**). Dexamethasone and betamethasone are two glucocorticoids with the highest anti-inflammatory activity. If cortisol has anti-inflammatory activity defined as 1, then prednisone, prednisolone, triamcinolone, and 6α-methylprednisolone have 4–5 times stronger anti-inflammatory properties, with longer half-life than cortisol. Examples of representative glucocorticoids and their properties are shown in **Table 1**.

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

Table 1.
Characteristics of representative corticosteroids [5].

1.2 Functions and activity of glucocorticoids

The two key roles glucocorticoids play as biological and pharmaceutical compounds are anti-inflammatory and immunosuppressive roles. Glucocorticoids also affect:

1. Carbohydrate and protein metabolism. Glucocorticoids stimulate the liver to form glucose in biochemical reaction (gluconeogenesis) from amino acids and glycerol or/and stimulate the liver to release glucose from glycogen. At the same time, the diminishing of glucose is reduced, reaction of lipolysis and protein breakdown increases, and as a result the blood glucose level rises. Patients suffering from diabetes or other forms of hyperglycemia during glucocorticoid therapy should be under special control. Glucocorticoids induce increased protein metabolism and deliver compounds such as amino acids for further reactions.

2. Lipid metabolism. One effect of therapy with corticosteroids is redistribution of fat tissue known as Cushing's syndrome.

3. Water and electrolyte balance. Glucocorticoids exert negatively on metabolism of Ca^{2+} due to reduction of absorption from the digestive system and increased excretion via kidneys. Prophylaxis of osteoporosis requires supplementation of Ca^{2+} ions and physical activity adequate to possibilities of patient. Additionally, glucocorticoids reduce activity of osteoclasts and stimulate the activity of osteoblasts. Glucocorticoid therapy sometimes may cause increased retention of Na^{+} ions and decrease in concentration of K^{+} ions because of interaction with receptor for mineralocorticoids. The deterioration in ion level may affect the cardiovascular system.

4. Impaired wound healing. Due to reduction of synthesis of collagen, glycosaminoglycans and disturbance in fibroblast function problem with healing wound may occur.

5. Anti-inflammatory and immunosuppressive activity. Glucocorticoids can suppress or prevent inflammatory reactions in different ways: reduction in diapedesis of granulocytes and proliferation of lymphocytes Th, inhibition/

reduction of activation of macrophages, neutrophils, mast cells and cytokines (interleukins 1, 2, 3, 4, 5, 6, 8), and tumor necrosis factor alpha (TNF-α); reduction in the expression of cyclooxygenase 2 (COX-2) resulting in dropping of production of a few prostanoids; intensification of activity of catechol amines; and reduction in production of histamine by basophils [7, 8].

Sometimes glucocorticoid treatment in the otorhinolaryngological diseases requires high doses or long time of therapy. It may cause adverse effects. Some of them are listed below:

1. Repression in responding on infections and injuries
2. Propensity to opportunistic infections
3. Propensity to hyperglycemia
4. Muscular dystrophy
5. Cushing's syndrome
6. Glaucoma (mostly in patients genetically predisposed)
7. Osteoporosis

Acute discontinuation of treatment may cause adrenocortical insufficiency, especially when therapy was long-term. It is important to reduce the dose of glucocorticoids slowly, not suddenly [5].

1.3 Pharmacokinetics of glucocorticoids and studies on animal model

Many factors have an impact on pharmacokinetics of drugs. Pharmacokinetics is described by acronym *LADME (liberation, absorption, distribution, metabolism, and elimination*). Firstly, the therapeutic (or its carrier) must be water-soluble, because of distribution in the blood. The protein binding of drugs is one of the key factors in initial parts in pharmacokinetic process. The greater the protein binding of drug is, the longer the activity of therapeutic due to its function as a stock of drug in the organism. Absorption depends on lipophilicity and solubility of drugs. According to the data and publications, only a few medical substances can effectively be used in otorhinolaryngological practice due to achieving sufficient concentration in the inner ear [9]. Two main groups of drugs are used in clinical practice: aminoglycoside (mainly gentamicin) in pharmacotherapy of Meniere's disease [10] and corticosteroids (dexamethasone, triamcinolone and dexamethasone) in pharmacotherapy of *idiopathic sudden sensorineural hearing loss* (ISSHL) and other cases of acute hearing loss [11]. The inner ear from a pharmacokinetic point of view is a multicompartment model [12, 13] with stable fluids and balance between them (due to the presence of *blood-labyrinth barrier* (BLB)). Distribution process depends on many different factors such as route of administration, model of administration (single or repeated administration), dose of medicine, ionic composition, and pH or osmolarity of solution. The same factors of drug chemical and physical properties influence the elimination of drug from the organism (clearance, rate of removal).

In a study published in 2017, authors in animal model (guinea pig) compared dexamethasone with saline. Both substances were administrated intravenously 60 min before implantation. As a final conclusion, authors stressed that

dexamethasone could reduce scarring process as the electrode negotiated the hook region or near the electrode tip, but they did not observe the relation between dexamethasone and reduction of fibrosis relating to cochleostomy [13]. In vitro studies showed the correlation between reduction (loss) of auditory cells after exposure to *tumor necrosis factor* alpha (TNF-alpha) and dexamethasone-releasing polymer used to coat electrode of cochlear implant carries.

Research carried out on animal model proved that prolonged steroid therapy could significantly improve hearing preservation rate (including pharmacokinetic and morphological analysis) when the electrode of cochlear implants was covered with dexamethasone (special formulation with controlled drug release) [14]. However, Honeder et al. did not confirm that steroids could have a positive impact on residual hearing in a guinea pig model. One reason why both authors gain different results may lie in different types of steroid therapy. In the first study, dexamethasone was used on the contrary to the second study where triamcinolone was administrated [15]. Douchement et al. investigated the effects of steroids using a gerbil animal model. Animals were implanted with an electrode with controlled dexamethasone delivery (1 and 10% concentration of dexamethasone) on one side and a conventional electrode on the contralateral side. Hearing levels were established based on the tone bursts on auditory brain stem responses at 4–6-week postimplantation and at 1-year postimplantation period for older gerbils. A 1-year observation period showed significantly improved results obtained for the high auditory frequencies, but the results for the low frequencies were ambiguous [16].

Cho et al. analyzed the efficacy of preoperative and intraoperative schemes of administration of steroids for hearing preservation. Dexamethasone was administrated systematically at the dose of 5 mg/ml in the preoperative period and then topically (off-label) during cochlear implantation surgery. Pure tone audiometry (PTA) was measured in four frequencies: 250, 500, 1000, and 2000 Hz. Statistically significant differences were observed between the steroid group and the control group, supporting the observation and beneficial impact of administration steroid treatment [17].

1.4 Glucocorticoid administration: the possibilities

During treatment of otologic diseases, two routes of administration of glucocorticoids are possible: local and systemic. Local administration (e.g., transtympanic injection) allows to achieve high concentration of glucocorticoid in the middle ear, but due to presence of Eustachian tube, the medication may be partly evacuated. Local drug administration to the middle and inner ear avoids "the first pass effect." The main advantages of local drug delivery are as follows:

1. Reduction dose of medicine

2. Achieving high concentration

3. Better effects of treatment

4. Reducing possibility of adverse effects

5. Bypassing of the blood-labyrinth barrier (BLB)

Local drug administration may involve intracochlear administration (e.g., stem cell, gene therapy) or extracochlear administration (e.g., intratympanic injection). A combination of both routes of drug delivery to the ear is also possible [13]. According to publications, systemic administration in treatment of otorhinolaryngological

diseases is known as noninvasive route of drug delivery, due to lack of damaging of tympanic membrane. Adverse effects of systemic delivery may be one of the purposes of discontinuation of the therapy. The presence of *blood-labyrinth barrier* (BLB) in the inner ear is one of the causes of problems with reaching high concentration of drug.

1.5 The experience in using glucocorticoids in PDT patients

This study was the first study which was carried out in the Institute of Physiology and Pathology of Hearing World Hearing Center and will be continued with different groups of patients and different implants and algorithms of glucocorticoid administration. The aim of the study was to evaluate different regimes of administration of glucocorticoids: dexamethasone and dexamethasone/prednisone to *partial deafness* treatment (PDT) patients who underwent cochlear implantation on the hearing preservation. Implant used in the study was the MED-EL implant with an electrode length of 28 mm (Flex 28). The impact of administrated glucocorticoids on hearing was measured in six different periods:

1. Preoperatively
2. During activation of audio processor
3. One month after activation of audio processor
4. Six months after activation of audio processor
5. Nine months after activation of audio processor
6. One year (12 months) after activation of audio processor

Forty-six patients were enrolled to the trial and then divided randomly into three subgroups. Patients from the first subgroup underwent intravenous steroid therapy (**Figure 1**). According to the scheme, 30 min before implantation, dexamethasone at the dose of 0.1 mg/kg body mass was administrated intravenously to patients from the first subgroup. For the next 3 consecutive days in every 12 h, dexamethasone was administrated intravenously at the same dose to each patient.

Patients from the second subgroup underwent prolonged (combined) steroid therapy: oral and intravenous. Three days prior to the surgery, prednisone was administrated orally at a dose of 1 mg/kg body mass/day. Then, 30 min before the cochlear implantation surgery, dexamethasone was administrated intravenously at a dose of 0.1 mg/kg body mass. For the next 3 consecutive days in every 12 h, dexamethasone was administrated intravenously (the same as in the first subgroup). For the next 3 days, prednisone was administrated orally at the dose of 1 mg/kg body mass/day. After this period, the dose of prednisone was reduced (10 mg per every

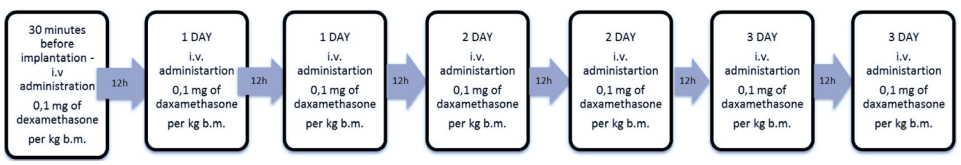

Figure 1.
Scheme of steroid administration in the first subgroup of patients.

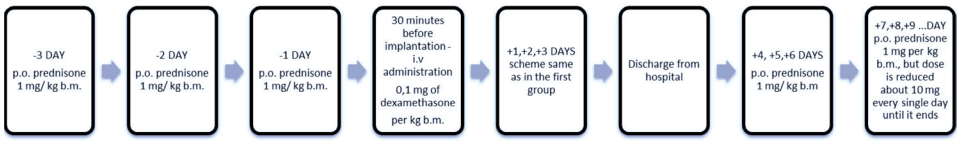

Figure 2.
Scheme of steroid administration in the second subgroup of patients.

day) till complete reduction of dose, due to reducing the risk of adverse effects. The algorithm of administration of glucocorticoids to patients form the second subgroup is presented below (**Figure 2**).

The third subgroup was a control group and underwent standard cochlear implantation procedure [18].

1.6 Administrated glucocorticoids

According to the protocol of this study, two different algorithms of administration with two different glucocorticoids were proposed in the study. Although both substances belong to the same pharmacological group, both of them have different pharmacokinetics and pharmacodynamic properties. Dexamethasone is a synthetic glucocorticoid (*molecular weight 392.46 g/mol*) with anti-inflammatory, anti-allergic, and immunomodulating activity. In common practice dexamethasone is administrated *intravenously* or off-label, e.g., *transtympanic injections*. After *intravenous* administration the mean time to peak concentration (C_{max}) is between 10 and 30 min, and the half-life ($t_{1/2}$) is from 2.2 to 3.8 h. Transport proteins are responsible for transport and distribution of dexamethasone in blood. Dexamethasone is mainly metabolized by the liver and eliminated with the bile. Only 2.6% of the chemically unchanged dose is eliminated via kidneys.

Prednisone is a synthetic glucocorticoid (derivative of cortisone) and classified according to the *Anatomical Therapeutic Chemical (ATC) Classification System* as H02 AB 07. Prednisone is *prodrug* which converts into *active metabolite—prednisolone* (higher anti-inflammatory activity). According to characteristic of medical product and literature data, bioavailability of prednisone administrated orally is between 70 and 90%. The mean time to peak concentration (C_{max}) is between 1 and 2 h. Half-life ($t_{1/2}$) is between 3.4 and 3.8 h in plasma and 18–36 h in tissue. Binding prednisone with plasma proteins is between 70 and 73% (binding prednisolone (active metabolite) to the plasma proteins is higher (90–95%)). Similar to dexamethasone, prednisone is metabolized mainly by the liver and eliminated with the bile. Pharmacodynamic and pharmacokinetic data were based on characteristics of medical products: dexamethasone and prednisone.

1.7 Methodology of the study: primary and secondary outcomes and inclusion and exclusion criteria

The primary outcome variables were mean values of hearing thresholds averaged across all 11 frequencies (125–8000 Hz). The secondary outcome variable was hearing preservation (HP). Hearing preservation (HP) was calculated by comparing hearing thresholds in the 1-year postoperative period with the preoperative hearing thresholds, according to the hearing preservation (HP) formula (below) and converted to three levels: minimal, partial, and complete hearing preservation.

$$HP = \left(1 - \frac{PTApost - PTApre}{PTAmax - PTApre}\right) * 100\ [\%] \quad (1)$$

In this equation, *PTApre* is the pure tone average measured preoperatively, *PTApost* is the pure tone average measured postoperatively, and *PTAmax* is the maximal sound intensity generated by a standard audiometer, usually 120 dB hearing level (HL), and *HP* is the rate of hearing preservation in percentage [19].

The protocol of this prospective clinical trial was approved by the Bioethics Commission. Patients enrolled to the study suffered from severe-to-profound hearing loss and were classified according to Prof. H. Skarżyński *partial deafness treatment (PDT) classification* into two groups: *partial deafness treatment-electrical* stimulation (PDT-EC) and *partial deafness treatment-electroacoustic* stimulation (PDT-EAS) (**Figure 3**) [20, 21].

Inclusion and exclusion criteria were in accordance with the consensus of the international *HEARRING* group on hearing preservation in cochlear implant. Study eligibility criteria included participants ≥18 years of age with a cochlear duct length of ≥27.1 (measured by computer tomography), with:

1. Hearing sound levels in the range of 10–120 decibels (dB) and sound frequencies of 125–250 hertz (Hz)

2. Hearing sound levels of 35–120 dB and frequencies of 500–1000 Hz

3. Hearing sound levels of 75–120 dB and frequencies of 2000–8000 Hz [18]

Exclusion criteria included suffering from severe diseases when the steroid treatment could worsen the patient's condition or when there would be a possibility of interaction between medication intake by patients and steroids. Nonparametric tests were used in the study due to discrepancies in the number of participants between all subgroups, small number of participants in the study, and violation of normal distribution of pure tone audiometry results [18].

1.8 Main results and observations

Preoperative hearing threshold levels of patients from the first, the second, and the control subgroup were similar. The difference between patients from the three subgroups was not statistically significant, which means that hearing

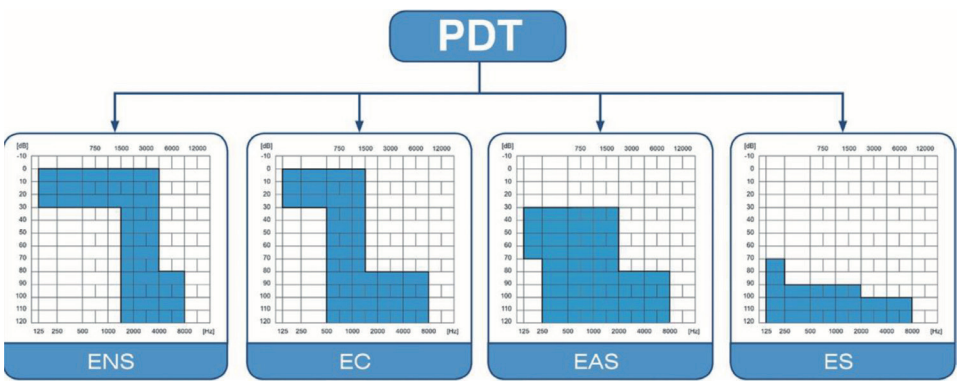

Figure 3.
Partial deafness treatment groups for cochlear implantation. ENS, electro-natural stimulation; EC, electrical complement; EAS, electrical-acoustic stimulation; ES, electrical stimulation.

thresholds in preoperative period of all participants, who were enrolled to the study, were similar.

The deterioration of average hearing thresholds (measured by pure tone audiometry) was observed from the first point of observation—the activation period. A significant difference was observed between two groups: patients from the second subgroup (combined steroid therapy, prednisone + dexamethasone) and the control subgroup. Patients from the second subgroup had better pure tone audiometry (PTA) results considering low frequencies in comparison with the results of patients from the control group. Similar observation was done in 1, 6, 9, and 12 months after activation follow-up periods. The results of the study may be even more a promise and beneficial for patients. The hearing of participants of the study, to whom combined (prolonged) glucocorticoid therapy was administrated, remained stable during all observed follow-up periods (*activation, 1-month, 6-month, 9-month, and 12-month post-activation follow-ups*), and they did not vary significantly (**Figure 4**).

The hearing preservation (HP) rate is calculated using hearing preservation formula by comparing hearing threshold in the 12-month postoperative period with the preoperative hearing thresholds. Then the results were divided, according to the hearing preservation (HP) formula, into minimal HP, partial HP, and complete HP according to **Table 2**. The smallest variability of results was observed in the second subgroup (patients to whom prednisone and dexamethasone were administrated) as well as the highest overall HP rate. Patients from the second subgroup (prolonged steroid therapy) and nearly 69% of the patients from the first subgroup had partial or complete hearing preservation. The majority of patients from the control group had minimal hearing preservation (**Table 2** and **Figure 5**).

1.9 Final conclusion

This study is the first study to report the results of two different regimes of steroid administration in human subjects who underwent cochlear implantation in comparison with the control group. As it was said in the previous paragraph, the findings of this study have shown that glucocorticoid therapy not only stabilizes hearing thresholds but also preserves hearing ability in adult patients. The combination of *intravenously* administrated dexamethasone and *orally* administrated prednisone in one scheme of administration seems to be the optimal treatment regimen.

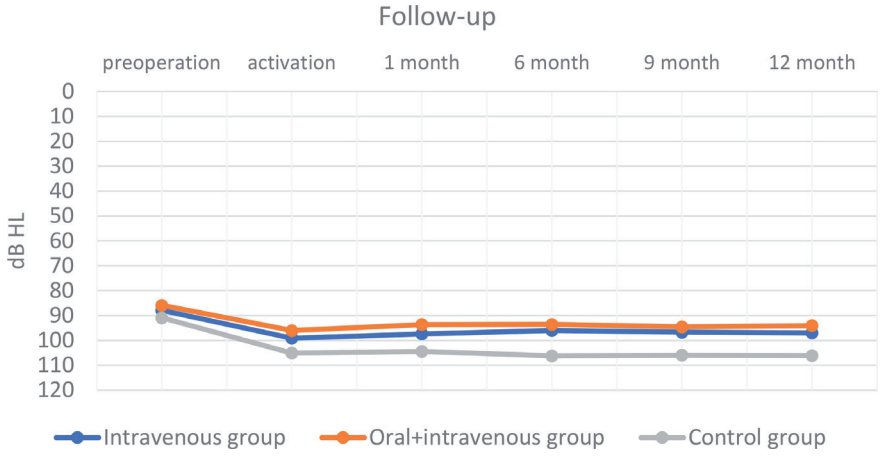

Figure 4.
Mean hearing thresholds of patients with standard steroid therapy (subgroup No 1), patients with prolonged steroid therapy (subgroup No 2), and control patients (subgroup No 3) in the preoperative period, upon activation, and at 1-month, 6-month, 9-month, and 12-month follow-up after CI implantation.

	Minimal (0–25%)	Partial (26–75%)	Complete (≤75%)
Subgroup No 1	5 (31.2)	7 (43.8)	4 (25.0)
Subgroup No 2	0 (0.0)	8 (61.5)	5 (38.5)
Control group	12 (70.6)	3 (17.6)	2 (11.8)

Table 2.
Hearing preservation 12 months after CI implantation, according to the type of treatment (data are given as the number of patients (percentage in brackets).

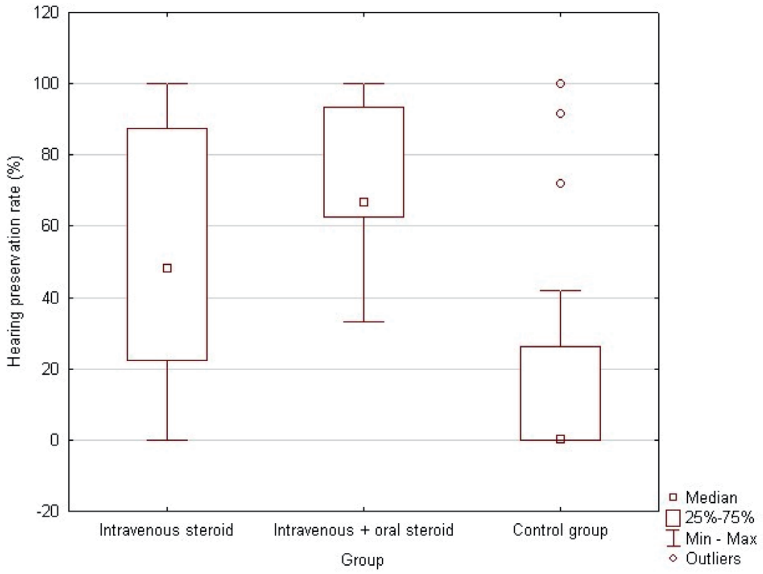

Figure 5.
Hearing preservation (HP) rate in three subgroups.

Previously published studies have shown that there have been new directions in the development and use of electrodes and cochlear implant surgery in recent years. Currently, researchers, clinicians, and commercial companies are working on developing modern steroid-eluting electrodes or electrodes with controlled drug delivery. The results of the preliminary study described in this chapter suggested that combined glucocorticoid administration (according to scheme of administration in the second subgroup) is beneficial in preserving and stabilizing hearing thresholds in patients undergoing cochlear implantation surgery. The findings of this study are supported by the results of similar studies [1, 17]. However, the present study adds to the findings of previous studies by having a relatively long follow-up period, of 12 months after activation, with study analysis conducted during six different follow-up periods. According to the results, administration of glucocorticoids (dexamethasone and prednisone or dexamethasone only) to the patients, who suffered from partial deafness and underwent cochlear implantation surgery, may be important in stabilization of hearing thresholds and in protection of hearing. The dispersion of measured values in the second group (the second subgroup) was lesser than in the first and the control group.

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