The Effect of Intracochlear and Intratympanic Dexamethasone on Cochlear Implant Impedance

Original Investigation

Fazıl Necdet Ardıç[1], Gökçe Aydemir[1], Funda Tümkaya[1], Ece Altınöz[1], Hande Şenol[2]

[1]Department of Otolaryngology-Head and Neck Surgery, Pamukkale University Faculty of Medicine, Denizli, Turkey
[2]Department of Biostatistics, Pamukkale University Faculty of Medicine, Denizli, Turkey

Abstract

Objective: This study investigated the impact of different local corticosteroid applications on impedance measurements in patients with cochlear implants.

Methods: The study was designed as a controlled, randomized, and prospective study in which 34 consecutive patients who had undergone cochlear implant surgery were divided into three groups. The first group received intracochlear dexamethasone, in the second group the middle ear cavity was filled with dexamethasone, and the third group did not receive dexamethasone. Intraoperative, postoperative 1st week, 1st month, 3rd month, 6th-month neural response telemetry, and impedances were measured. The measurements were compared by electrode groups representing the different regions of cochlea like basal (1–7), middle (8–13), and apical (14–22) regions.

Results: The intergroup analysis showed no statistically significant differences in impedance measurements of the basal, middle, and apical regions ($p>0.05$). However, the impedances were lower in the two dexamethasone groups, especially in the basal and middle parts. Sixth month impedances were also lower in the dexamethasone groups. There was apparent stability in the impedance of the basal region with the intracochlear application during the first week.

Conclusion: Local dexamethasone applications had a potentially positive impact on the impedance of the basal and middle regions. Patients had lower impedances than the control group during follow-up and at the endpoint. The increase in the apical region may indicate that dexamethasone was not reaching the apical zone in local applications.

Keywords: Cochlear implants, dexamethasone, electrode impedance, fibrosis

ORCID IDs of the authors:

F.N.A. 0000-0003-4230-3141;
G.A. 0000-0002-9780-4413;
F.T. 0000-0002-3213-8106;
E.A. 0000-0002-4163-9586;
H.Ş. 0000-0001-6395-7924.

Cite this article as: *Ardıç FN, Aydemir G, Tümkaya F, Altınöz E, Şenol H. The Effect of Intracochlear and Intratympanic Dexamethasone on Cochlear Implant Impedance. Turk Arch Otorhinolaryngol 2023; 61(3): 103-108*

Corresponding Author:
Fazıl Necdet Ardıç;
fnecdetardic@gmail.com

Received Date: 17.06.2023
Accepted Date: 12.08.2023

DOI: 10.4274/tao.2023.2023-6-4

Introduction

One of the common problems with a cochlear implant is the decrease in effectiveness over time due to physiological and mechanical damage in the cochlea (1). The short- and long-term effects of inflammation, osteoneogenesis, and fibrosis limited to the basal turn after surgery have been considered in this condition (2, 3). This is caused by a fibrotic capsule forming around the implant, which in turn results in an immune response to surgical trauma or a foreign body reaction to the platinum-iridium and silicon used in cochlear implants (4, 5). Studies have also shown a correlation between fibrotic tissue and electrode impedance (6). Choi et al. (7) suggested that impedance measurement could be used as a biomarker for cochlear damage.

Animal studies showed that glucocorticoids reduced foreign body reactions and fibrosis, thus increasing the lifespan of the spiral ganglia and the hair cells (8). Corticosteroids have been used for many years in cochlear implant surgeries. Although different systemic and local administration routes have been reported, it is still under development today (9-11).

We aimed to observe the effect of local corticosteroid applications during cochlear implant surgery on impedance.

Methods

A controlled, randomized, prospective clinical trial was planned in patients with cochlear implant surgery (registered with clinicaltrials.com, no: NCT04397354). Pamukkale University Non-invasive Clinical Research Ethics Committee approval was obtained (no: 60116787-020/20945, date: 23.03.2018). All patients signed the written informed consent form. Those with cochlear anomalies were excluded.

Cochlear implant operation was performed under general anesthesia, and 1 mg/kg methylprednisolone was administered intravenously to all patients in addition to anesthetic drugs as a part of routine general anesthesia. The round window soft technique was used to implement the devices. The cases with cochleostomy were excluded. The same cochlear implant electrode model was used in all patients (Cochlear, Inc. CI 422). The cochlear implants were activated after one month.

The patients were randomly divided into three groups for implantation using the random number table method according to the administration of dexamethasone (dex) (4 mg/mL).

1. In the first group, dex was administered slowly with a 27-gauge needle into the cochlea after a round window membrane incision (Group 1, the Cocdex group).

2. In the second group, dex was administered into the middle ear after a round window membrane incision (Group 2, the Middex group).

3. Dex was not administered to the third group (Group 3, control, the Nodex group).

The drug was left in place for three minutes before inserting the electrodes.

Intraoperative neural response telemetry thresholds and impedances were measured. Impedance measurements were repeated at the end of the first postoperative week, and at the first third, and sixth months. Monopolar1+2 (MP1+2) impedance (kOhm), measurements were used for comparison.

The mean of the basal (1–7), middle (8–13), and apical (14–22) electrodes were used for comparison. We also compared the average of all electrodes. The Custom Sound EP 5.0 (5.0.4.136) program provided by Cochlear, Inc. was used for measurement.

Statistical Analysis

All statistical analyses were performed with the SPSS 25.0 software [IBM SPSS Statistics 25 software (IBM Corp.: Armonk, NY, USA)]. Continuous variables were expressed as mean ± standard deviation, median (minimum-maximum values), and categorical variables as number and percent. The Shapiro–Wilk test was used to test for normality. If parametric test conditions were satisfied, the One-Way Analysis of Variance (post-hoc: Tukey test) was used to compare groups. If parametric test conditions were not satisfied, Kruskal–Wallis variation analysis (post-hoc: The Mann–Whitney U test with Bonferroni correction) was used to compare the groups. For pairwise comparisons, if parametric test conditions were satisfied the Repeated Measures ANOVA (post-hoc: Bonferroni test), and if parametric test conditions were not satisfied, the Friedman (post-hoc: Wilcoxon signed-rank test with Bonferroni correction) tests were used. The chi-square test was used to compare categorical variables and $p<0.05$ was considered statistically significant.

Results

Initially, a total of 34 patients were included in the study. Of these, 12 were in Group 1, 12 were in Group 2, and 10 were in Group 3. One patient in Group 1 and one patient in Group 3 were excluded from the study due to noncompliance with follow-up and repetitive measurement times. Three patients in Group 3 in whom the cochleostomy technique was used were also excluded. Due to the pandemic, the 1st-week measurement of one patient, the 1st-month measurement of one patient, the 3rd-month measurement of two patients in Group 1; the 1st-month measurement of one patient, the 3rd-month measurement of one patient in Group 2; and the 1st-week measurements of two patients, the 1st-month measurement of one patient in Group 3 could not be performed on the planned date, the values of these measurements were not used in the analysis (Figure 1).

There were no differences between the groups regarding gender (17 women and 12 men, $p=0.543$) and age ($p=0.688$).

The variations of the mean MP1+2 impedance measurements over time are given in Figure 2.

In the apical zone, impedances reached the highest level, usually at the end of the first month, except in the Cocdex group, and then decreased rapidly in all groups.

In the basal and middle zones, all three groups reached the maximum impedance value at the end of the first month. In the first week, the impedances measured from the basal region were lowest in the intracochlear group (Figure 2). In the first month, impedances were higher in the Nodex group compared to the two dex groups in the basal and middle regions (Figure 2). The statistical comparisons of the time points within the groups are also plotted in Figure 2. Impedances increased until the first month (between t0 and t2) in all regions except for the basal and middle electrodes of the Cocdex roup ($p>0.05$), and these increases were statistically significant ($p<0.05$).

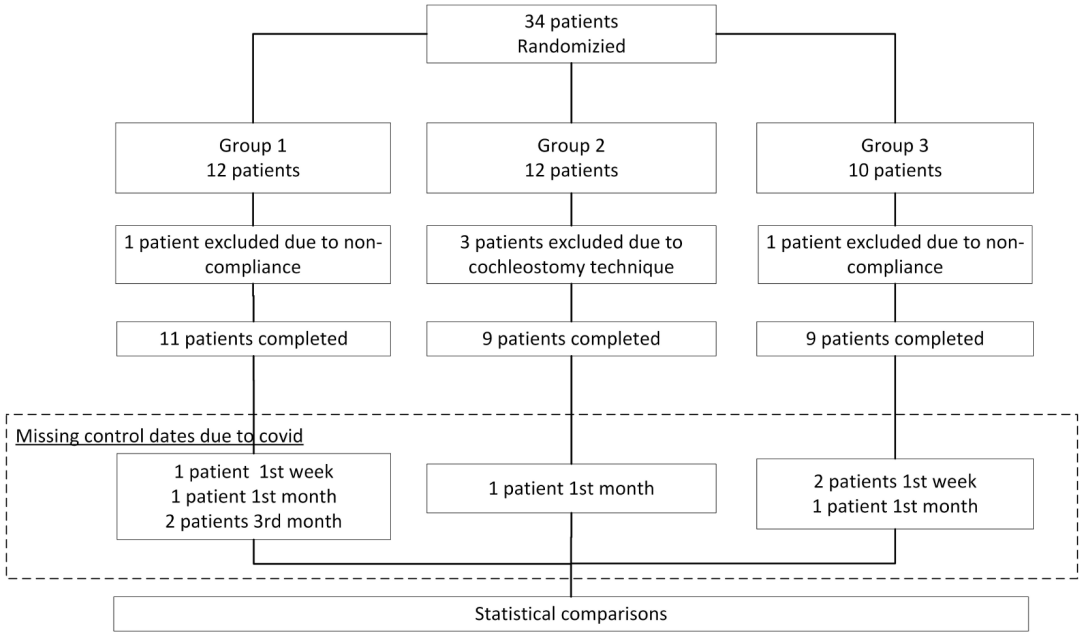

Figure 1. Study design, patient groups, and missing control points

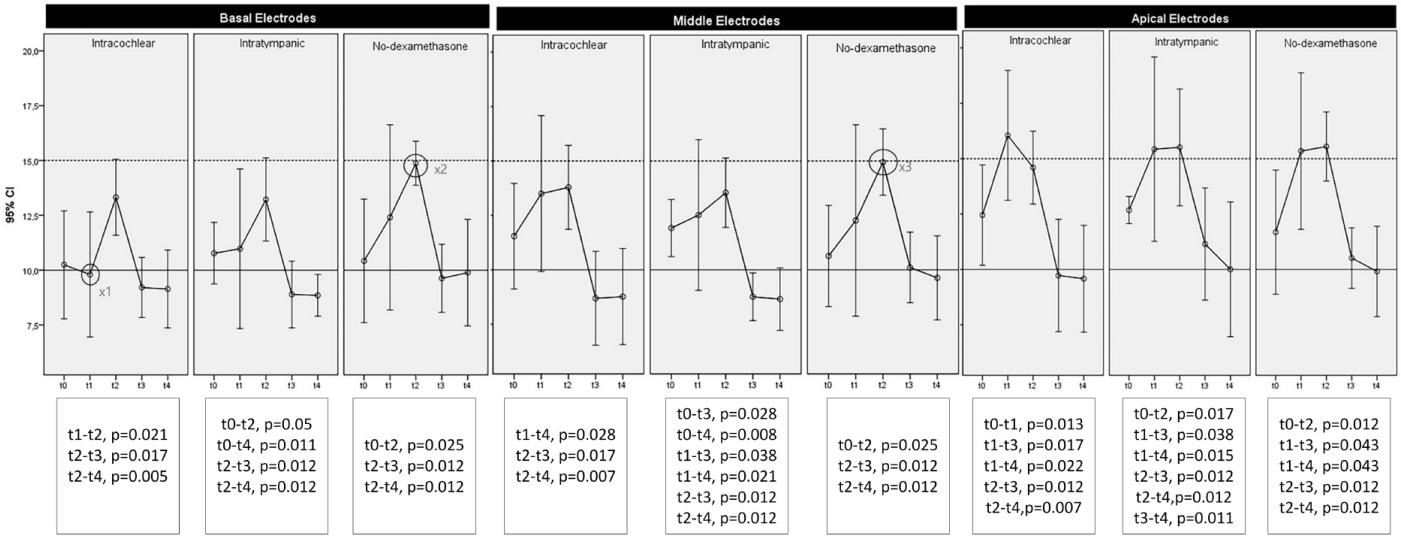

Figure 2. MP 1+2 impedances were compared within groups according to the regions of the cochlea. In the first week, the impedances measured from the basal region were lowest in the intracochlear group (x1). In the first month, impedances were the highest in the Nodex group compared to the two dexamethasone groups in basal and middle regions (x2, x3). The impedance increased until the first month (between t0 and t2) in all regions, and the increases were statistically significant ($p<0.05$), except for the basal and middle electrodes of the Cocdex group ($p>0.05$). In the sixth-month control, impedances were lower in the dexamethasone groups than in the control group. Statistically significant comparisons between time points within the groups are plotted below the graphics (Wilcoxon signed-rank test) (t0: during surgery, t1: first week, t2: first month, t3: third month, t4: sixth month)

No statistically significant results were found between the groups at any time point or in any region ($p>0.05$) (Table 1). The change in the apical region in the 1st week was not significantly faster than in the middle and basal parts. The impedances were lower in the first week in the middle and basal regions. Their highest values were measured at the end of the first month in all three groups. Impedances were higher in the Control (Nodex) group but were not statistically significant ($p>0.05$).

There were also no statistically significant differences when the mean impedances of all electrodes were compared ($p>0.05$).

Table 1. Age and MP1+2 data plotted according to groups

	Group 1 (n=11)						Group 2 (n=9)						Group 3 (n=9)						Kruskal–Wallis sig
	Mean	SD	min	max	med	STE	Mean	SD	min	max	med	STE	Mean	SD	min	max	med	STE	
Age(month)	182.18	192.24	14	604	115	57.96	248.44	244.98	13	741	279	81.66	267.66	238.07	24	660	237	79.37	p=0.688
MP1+2 apikal t0	12.09	2.14	7.86	15.42	12.52	0.65	12.49	0.89	10.98	14.03	12.52	0.30	12.05	2.24	6.34	13.68	12.81	0.75	p=0.959
MP1+2 apikal t1	15.20	3.50	8.85	20.57	15.78	1.11	15.54	4.67	7.25	24.73	16.47	1.56	15.05	3.18	9.63	19.13	15.36	1.20	p=0.972
MP1+2 apikal t2	14.15	2.40	9.05	16.60	14.52	0.76	15.51	3.15	11.31	22.42	15.28	1.11	15.63	1.48	13.39	17.30	15.83	0.52	p=0.362
MP1+2 apikal t3	10.71	3.10	6.74	15.02	11.03	1.03	11.32	2.88	7.93	17.90	10.80	0.96	10.41	1.37	8.23	11.82	10.67	0.46	p=0.904
MP1+2 apikal t4	10.42	2.50	5.65	13.45	10.21	0.75	9.74	3.49	7.24	18.34	8.13	1.16	9.72	1.69	8.07	13.06	9.11	0.56	p=0.420
Friedman test sig	p=0.001						p=0.006						p=0.006						
MP1+2 middle t0	11.14	2.26	6.75	14.03	11.91	0.68	11.69	1.62	9.75	14.00	11.71	0.54	11.00	1.88	6.78	12.63	11.62	0.63	p=0.796
MP1+2 middle t1	12.52	4.33	5.23	18.86	12.54	1.37	12.75	3.93	5.71	15.97	14.56	1.31	11.99	3.90	6.64	17.06	12.38	1.47	p=0.925
MP1+2 middle t2	13.37	2.77	7.45	15.86	14.24	0.87	13.54	1.91	9.83	15.51	14.12	0.67	14.81	1.52	12.78	16.36	15.39	0.54	p=0.315
MP1+2 middle t3	9.92	3.17	5.53	14.28	8.81	1.06	9.13	1.65	6.79	12.10	9.18	0.55	9.99	2.36	5.99	13.99	10.00	0.79	p=0.776
MP1+2 middle t4	9.63	2.51	5.23	12.49	10.86	0.76	8.44	1.73	6.59	11.12	8.83	0.58	9.50	2.52	6.17	13.89	9.65	0.84	p=0.517
Friedman test sig	p=0.001						p=0.002						p=0.038						
MP1+2 basal t0	10.25	2.41	5.48	13.48	10.94	0.73	10.51	1.75	8.44	13.04	9.69	0.58	10.92	2.35	5.49	13.31	11.16	0.78	p=0.712
MP1+2 basal t1	9.82	3.57	5.57	15.96	8.88	1.13	10.52	4.29	4.89	14.76	10.79	1.43	11.84	3.97	7.48	17.62	10.41	1.50	p=0.591
MP1+2 basal t2	12.90	2.80	6.44	15.43	13.89	0.89	13.22	2.27	8.68	16.06	13.81	0.80	14.44	1.55	11.17	15.77	15.07	0.55	p=0.247
MP1+2 basal t3	10.25	2.45	7.89	14.36	9.06	0.82	9.51	2.52	5.88	14.46	9.65	0.84	9.67	2.59	6.93	15.09	9.76	0.86	p=0.708
MP1+2 basal t4	9.54	2.38	6.17	14.02	9.40	0.72	8.84	1.07	6.57	10.26	8.77	0.36	9.61	2.66	6.27	13.36	10.07	0.89	p=0.720
Friedman test sig	p=0.009						p=0.006						p=0.032						
MP1+2 total t0	11.16	2.15	6.70	13.54	12.19	0.65	11.56	1.38	9.76	13.69	11.39	0.46	11.32	2.10	6.20	13.21	11.75	0.70	p=0.991
MP1+2 total t1	12.52	3.36	6.66	17.82	12.11	1.06	12.94	3.88	6.00	18.49	14.01	1.29	12.96	3.47	8.94	17.94	13.50	1.31	p=0.949
MP1+2 total t2	13.47	2.60	7.65	15.86	14.05	0.82	14.09	2.05	9.94	16.79	14.12	0.73	14.96	1.41	12.80	16.22	15.57	0.50	p=0.471
MP1+2 total t3	10.29	2.82	6.82	14.26	9.29	0.94	9.99	1.87	6.86	13.09	10.08	0.62	10.02	1.96	7.05	13.59	9.59	0.65	p=0.979
MP1+2 total t4	9.86	2.28	5.96	12.34	10.35	0.69	9.01	1.74	7.03	12.52	8.77	0.58	9.61	2.08	6.86	12.65	9.52	0.69	p=0.627
Friedman test sig	p=0.002						p=0.002						p=0.026						

t0: During surgery, t1: First week, t2: First month, t3: Third month, t4: Sixth month, SD: Standard deviation, STE: Standard error, sig: Significance, min: Minimum, max: Maximum, med: Median

Discussion

In this prospective, randomized, controlled study, we aimed to measure the effect of different dex applications on tissue inflammation during cochlear implantation by electrode impedance. We found that the intraoperatively measured impedances decreased in the long-term and reached the lowest point, mainly in the 6th month, which was the study time limit. Impedances were lower in the dex groups than in the control group in the basal and middle regions. The stability of impedance at basal electrodes in the first week of the Cocdex group was marked. The first-week impedances of the Middex group were also lower than those of the Nodex group. These findings may be attributed to the local and short-duration effects of corticosteroids. The sharp increase in impedance in the apical electrodes during the first week, even in the dex groups, may indicate that dex was not reaching the apical zones. In all groups, a marked decrease in impedances was observed after the first month, the cochlear implant's activation date. Again, the impedances of the dex groups decreased more than the those of the control (Nodex) group at the endpoint of the study.

A similar hypothesis was tested in guinea pigs. In this study the authors compared the effects of the intratympanic, intracochlear, and systemic administration routes by cytokines and residual hearing. They reported that the intracochlear route had reached the highest drug concentration. Intracochlear dex provided better protection for residual hearing and a less inflammatory response in the cochlea (10). We observed some promising results, especially in the basal region.

The results of animal and human studies with local steroid applications elicited the research on dex eluting electrodes. Astolfi et al. (12) tried a 10% dex eluting electrode on guinea pigs and reported that less tissue growth had been observed. Briggs et al. (3) implanted a dex eluting electrode and followed the patients for two years with MP1+2 impedance measurements. They found that the experimental electrode had lower impedance at all time points and all cochlea regions than the standard electrode. They observed a direct reduction of impedances even in the first week. Our study also found stability in the impedances in the basal region. After the effect of dex had diminished over time, the impedances rose again.

Additional systemic steroids used with dex eluding electrodes were tested (13). Systemic steroids did not show an additional effect over inserting electrodes alone. The authors concluded that the protective effect of steroids was prominent, especially in traumatic insertions. We could not obtain statistically significant results for the use of dex. Perhaps this was due to the atraumatic insertion technique in all patients. Ahmadi et al. (14) also support this conclusion. They said there must be trauma in the cochlea to see the effectiveness of dex. Non-traumatic insertion preserved the cochlea in most animals.

Lee et al. (2) compared different local and systemic applications in an animal implant model. They reported no significant differences between the delivery routes, but that could be effective if used for a longer duration and higher dose. The protective effect of dex had a linear relationship with the concentration of the drug and the time of contact with the round window. Chang et al. (9) reported that 2% dex for 60 minutes had the same protective effect with 20% dex for 30 minutes on guinea pigs.

We observed an increase in impedance in the apical region in the early period in both dex groups. Wei et al. (15) also observed the same increase in the 1st week with an early switch-on technique. In the 8th week, they showed that there was an increasing trend of impedance in all parts of the cochlea and was highest in the basal region. They argued that this was because fibrosis had started on days 2 to 5 after the operation, fibrotic tissue began to dissolve in the second week, and more severe fibrotic tissue formed in the basal region due to trauma. In our study, impedance remained low in the dex groups in the basal region. It might be due to the anti-inflammatory effect of the corticosteroids.

One of the limitations of this study was the coronavirus disease-2019 pandemic. Some patients missed the exact test dates, so we omitted some data from the calculations. Another limitation is the short time between dex administration and implant placement.

Nevertheless, this kind of study in patients is rare. Its advantages are that standard commercial electrodes were used, all operations were done by a single surgeon and the tests by a single audiologist, and only objective parameters were measured.

Conclusion

Although there were no significant differences among the groups, intracochlear and intratympanic applications of dex positively impacted the impedance in the basal and middle regions during the first week. Patients in the dex groups had lower impedances than the control group during follow-up and at the endpoint. The sharp increase in the apical region may indicate that dex was not reaching the apical zone in local applications.

Ethics Committee Approval: Approval was granted by the Pamukkale University Non-invasive Clinical Research Ethics Committee (no: 60116787-020/20945, date: 23.03.2018).

Informed Consent: All patients signed the written informed consent form.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: F.N.A., G.A., F.T., E.A., Concept: F.N.A., F.T., H.Ş., Design: F.N.A., G.A., F.T., H.Ş., Data Collection and/or Processing: F.N.A., G.A.,

E.A., Analysis and/or Interpretation: F.N.A., G.A., E.A., H.Ş., Literature Search: F.N.A., G.A., F.T., H.Ş., Writing: F.N.A., G.A., F.T.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Main Points

- Local dexamethasone applications had a possible positive impact on the impedance of the basal and middle regions.
- Patients in the dexamethasone groups had lower impedances than the control group during follow-up and at the endpoint.
- The impedance increase in the apical region may indicate that dexamethasone was not reaching the apical zone in local applications.

References

1. Scheper V, Hessler R, Hütten M, Wilk M, Jolly C, Lenarz T, et al. Local inner ear application of dexamethasone in cochlear implant models is safe for auditory neurons and increases the neuroprotective effect of chronic electrical stimulation. PLoS One 2017; 12: e0183820. [Crossref]
2. Lee MY, Kim YC, Jang J, Jung JY, Choi H, Jang JH, et al. Dexamethasone delivery for hearing preservation in animal cochlear implant model: continuity, long-term release, and fast release rate. Acta Otolaryngol 2020; 140: 713-22. [Crossref]
3. Briggs R, O 'Leary S, Birman C, Plant K, English R, Dawson P, et al. Comparison of electrode impedance measures between a dexamethasone-eluting and standard Cochlear™ Contour Advance® electrode in adult cochlear implant recipients. Hear Res 2020; 390: 107924. [Crossref]
4. Cho HS, Lee KY, Choi H, Jang JH, Lee SH. Dexamethasone is one of the factors minimizing the inner ear damage from electrode insertion in cochlear implantation. Audiol Neurootol 2016; 21: 178-86. [Crossref]
5. Wilk M, Hessler R, Mugridge K, Jolly C, Fehr M, Lenarz T, et al. ımpedance changes and fibrous tissue growth after cochlear implantation are correlated and can be reduced using a dexamethasone eluting electrode. PLoS One 2016; 11: e0147552. [Crossref]
6. Needham K, Stathopoulos D, Newbold C, Leavens J, Risi F, Manouchehri S, et al. Electrode impedance changes after implantation of a dexamethasone-eluting intracochlear array. Cochlear Implants Int 2020; 21: 98-109. [Crossref]
7. Choi J, Payne MR, Campbell LJ, Bester CW, Newbold C, Eastwood H, et al. Electrode impedance fluctuations as a biomarker for inner ear pathology after cochlear implantation. Otol Neurotol 2017; 38: 1433-9. [Crossref]
8. Kather M, Koitzsch S, Breit B, Plontke S, Kammerer B, Liebau A. Metabolic reprogramming of inner ear cell line heı-oc1 after dexamethasone application. Metabolomics 2021; 17: 52. [Crossref]
9. Chang A, Eastwood H, Sly D, James D, Richardson R, O'Leary S. Factors influencing the efficacy of round window dexamethasone protection of residual hearing post-cochlear implant surgery. Hear Res 2009; 255: 67-72. [Crossref]
10. Lyu AR, Kim DH, Lee SH, Shin DS, Shin SA, Park YH. Effects of dexamethasone on intracochlear inflammation and residual hearing after cochleostomy: a comparison of administration routes. PLoS One 2018; 13: e0195230. [Crossref]
11. Eastwood H, Chang A, Kel G, Sly D, Richardson R, O'Leary SJ. Round window delivery of dexamethasone ameliorates local and remote hearing loss produced by cochlear implantation into the second turn of the guinea pig cochlea. Hear Res 2010; 265: 25-9. [Crossref]
12. Astolfi L, Simoni E, Giarbini N, Giordano P, Pannella M, Hatzopoulos S, et al. Cochlear implant and inflammation reaction: safety study of a new steroid-eluting electrode. Hear Res 2016; 336: 44-52. [Crossref]
13. Chambers S, Newbold C, Stathopoulos D, Needham K, Miller C, Risi F, et al. Protecting against electrode insertion trauma using dexamethasone. Cochlear Implants Int 2019; 20: 1-11. [Crossref]
14. Ahmadi N, Gausterer JC, Honeder C, Mötz M, Schöpper H, Zhu C, et al. Long-term effects and potential limits of intratympanic dexamethasone-loaded hydrogels combined with dexamethasone-eluting cochlear electrodes in a low-insertion trauma guinea pig model. Hear Res 2019; 384: 107825. [Crossref]
15. Wei JJ, Tung TH, Li LP. Evolution of impedance values in cochlear implant patients after early switch-on. PLoS One 2021; 16: e0246545. [Crossref]