RESEARCH ARTICLE
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The Effect of Coenzyme Q10 on Vestibular Compensation Process after Unilateral Labyrinthectomy in Rats Using Behavioral Tests

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ABSTRACT

Objective: To determine the effect of coenzyme Q10 on the vestibular compensation process after unilateral labyrinthectomy.
Material and Methods: Thirty Wistar rats were randomly assigned to 3 equal groups: the negative control group, the experimental group and the control group. Labyrinthectomy surgeries were performed in all 3 groups. After the labyrinthectomy, findings such as nystagmus with its fast phase directed to the undamaged side, deviation of the head to the side operated on, impairment in walking, and decreased tonus of the extensor muscles on the same side were observed.
Results: The values of Group EG and Group CG were somewhat higher than those of Group NCG in terms of the degree of head tilt, but there was no statistically significant difference among the three groups. Although Group EG and Group CG were found to differ statistically significantly from Group NCG on certain days in terms of postural deficit values and nystagmus, this significance remained limited to those particular days.
Conclusion: The effect of CoQ10 on the vestibular compensation process was limited may be due to its limited dose, short duration of administration, and the limited number of rats. We believe that the effects of CoQ10 on the vestibular compensation process after labyrinthectomy should not be neglected. Despite the fact that we administered it at limited doses for a short term on a limited number of rats, CoQ10 should be used in larger samples, in higher doses, and for a longer time because CoQ10 has positive, though limited effects, on the vestibular compensation process.

Keywords: Labyrinthectomy, CoQ10, vestibular compensation

INTRODUCTION

In 1904, Millian and Lake independently identified labyrinthectomy, the last-resort treatment method for controlling vertigo (1, 2). Labyrinthectomy is divided into two categories as chemical and surgical labyrinthectomy. Aminoglycosides are used as vestibulotoxic agents in chemical labyrinthectomy to treat vertigo by performing unilateral vestibular ablation (3). Surgical labyrinthectomy is quite an effective ablative surgical method that can be used for vertigo control in unilateral peripheral vestibular pathologies after medical treatment failure and in the presence of significant hearing loss (1, 2).

Substances that prevent or delay the oxidation of biological molecules such as proteins, lipids, carbohydrates and DNA, which exist in the cellular structure and can be oxidized, are called antioxidants. The prevention of the oxidation of such molecules is called the antioxidant defense system (4, 5). Coenzyme Q10 (CoQ10) is a vitamin-like compound that acts as a coenzyme in key enzymatic reactions in cells during the production of energy. It can be found in every cell and dissolved in fat. Coenzyme Q10 interacts with oxygen-induced radicals and free oxygen, preventing the onset of lipid peroxidation and damage to biomolecules (6-8). In addition to its antioxidant

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effect, it has free radical scavenging and vasodilator effects. It also reduces pro-inflammatory cytokines and blood viscosity. Coenzyme Q10 has been cited in the literature as being used in the field of otolaryngology in patients with vertigo and Meniere's disease, in the treatment of sudden hearing loss, and in the treatment of tinnitus. It has also been used because of its protective effect against ototoxic agents (9-12).

The knowledge on vestibular functions stems from clinical information obtained from unilateral or bilateral labyrinthine lesions and experimental information obtained from animal experiments on this subject. Based on animal experiments, medications, as well as visual and physical exercises, affect the compensation event (13).

This study aimed to assess how parenteral use of CoQ10 affected the vestibular compensation process after labyrinthectomy depending on the degree of head tilt, postural deficit and nystagmus. A review of the literature showed numerous studies involving the treatment of vestibular compensation after labyrinthectomy, but no study involving the use of CoQ10.

MATERIALS AND METHODS

This study involved the use of 30 healthy adult female Wistar albino rats with an average weight of 200–250 grams. The rats were kept in appropriate ventilation conditions and special cages in rooms with sunlight. For seven days before the study began, the rats were housed at room temperature in an environment where they could get 12 hours of light, 12 hours of dark, with free access to food and water. The water they drank was replaced every day, and their cages were cleaned every other day. No dietary restrictions were administered before or during the study. Power analysis was carried out, and the number of rats in the sample for 3 units was determined to be at least 10 for each group based on mean difference, 80% testing power, 95% confidence interval and 2 standard deviations. This study was conducted with 1. Ondokuz Mayıs University Faculty of Medicine ethics committee approval (2016/16).

The 30 Wistar rats were randomly assigned to 3 equal groups: the negative control group (NCG) (n=10), the experimental group (EG) (n=10) and the control group (CG) (n=10). Labyrinthectomy surgeries were performed in all 3 groups.

Surgical intervention: Preoperative ampicillin sodium (20 mg/kg) was injected intra-muscularly for surgical infection prophylaxis. After anesthesia was administered intraperitoneally (IP) as ketamine 10% (50 mg/kg; Richter Pharma AG, Wels, Austria) and xylazine 2% (5 mg/kg; Bayer AG, Leverkusen, Germany), both ears of all rats were examined with the help of an otomicroscope. All rats in all 3 groups underwent surgical labyrinthectomy by the same surgeon on their right ears. Following a post-auricular incision, the submandibular gland and the facial nerve were identified, and the facial nerve was preserved by lateralizing the gland. Tympanic bulla was identified, and the bulla was exposed using a surgical electric drill and a curette. The malleus and the incus were identified. They were removed, and then the oval window and the vestibule were identified and destroyed by using an aspirator and a curette. The neuroepithelium and the membranous labyrinth were ablated using a curette and an aspirator. Finally, alcohol was injected and aspirated 3 times to completely destroy the vestibule. The wound site was stitched using 4.0 prolene sutures, and the sutures were removed 2 weeks later (Figure 1a-f). After the operation, the rats were each taken into a single cage and sheltered under standard conditions, with enough feed and water. The study excluded rats that lost more than 20% weight prior to treatment, developed ulcers in the cornea due to facial nerve damage, lost excessive blood intraoperatively or had symptoms such as convulsions, hemiataxia and paresis. During the study, none of

Figure 1a-f. Intraoperative images

the rats were lost. In the postoperative period, none of the rats had dehiscence, and there were no signs of infection.

The rats in the negative control group did not undergo any preoperative or postoperative medication. In the experimental group, 10 mg/kg CoQ10, dissolved in soybean oil, was administered as 1 mL for a single time per day intraperitoneally, for 3 days before the operation and for 3 days after the operation. In the negative control group, a single intraperitoneal dose of 1 mL soybean oil per day was administered, for 3 days before the operation and 3 days after the operation, to mimic the stress of IP injection that could occur in the rats in the experimental group.

Coenzyme Q10 Administration: Coenzyme Q10 powder (Sigma-Aldrich, Germany, Product Number: C9538-1G) was weighed in amounts for daily use, placed in bottles to protect it from light, wrapped with parafilm and stored at –20°C. The amount to be administered, a dose of 10 mg/kg daily, was dissolved in 1 mL soybean oil (Sigma-Aldrich, Germany) for each subject. After it was mixed in vortex for 10 minutes to obtain a homogeneous solution, it was pulled into injectors to be protected from light again and stored at +4°C (Figure 2a and 2b). The solution that was prepared was administered intraperitoneally for 3 days before and after the operation to the rats in EG. Soybean oil was administered to the rats in the control group intraperitoneally in the same dose and for the same duration. All injections were administered at the same time in the morning.

Evaluation of Vestibular Imbalance: After the labyrinthectomy, findings such as nystagmus with its fast phase directed to the undamaged side, deviation of the head to the side operated on, impairment in walking, and decreased tonus of the extensor muscles on the same side were observed, and the findings were recorded using a video camera (Figure 3a-d). Based on the study by Günther et al. (14), nystagmus, degree of head tilt and postural asymmetry were observed to assess behavioral signs of vestibular imbalance after labyrinthectomy on days 1, 2, 3, 7, and 15, and these behaviors were rated to have a score of a maximum of 10 points. The researchers observed the rats, and two researchers who did not know the group allocation of the rats scored the behavioral tests.

Figure 2a and 2b. Preparation of coenzyme Q10 with soybean oil

Nystagmus was observed visually.

- In the presence of spontaneous nystagmus, a score of 6–10 was given corresponding to 1 point per 60 beats per minute.
- If there was not any spontaneous nystagmus during rest, the animal was touched lightly. Such stimulated nystagmus was given a score of 1–5 corresponding to 1 point per 60 beats per minute.

The degree of head tilt was assessed spontaneously based on the angle between the jaw and the horizontal plane.

- If the angle was 90 degrees or if the head fell to the side of the lesion during rest and a barrel rolling, 10 points were given.
- If the angle was 60 degrees, 7 points were given.
- If the angle was 45 degrees, 5 points were given.

Postural asymmetry was scored as follows:

- Spontaneous barrel rolling was given 10 points.
- Barrel rolling that occurred after a light touch or blowing was given 9 points.
- Taking a lying position without any leg support toward the side of the lesion was given 8 points.

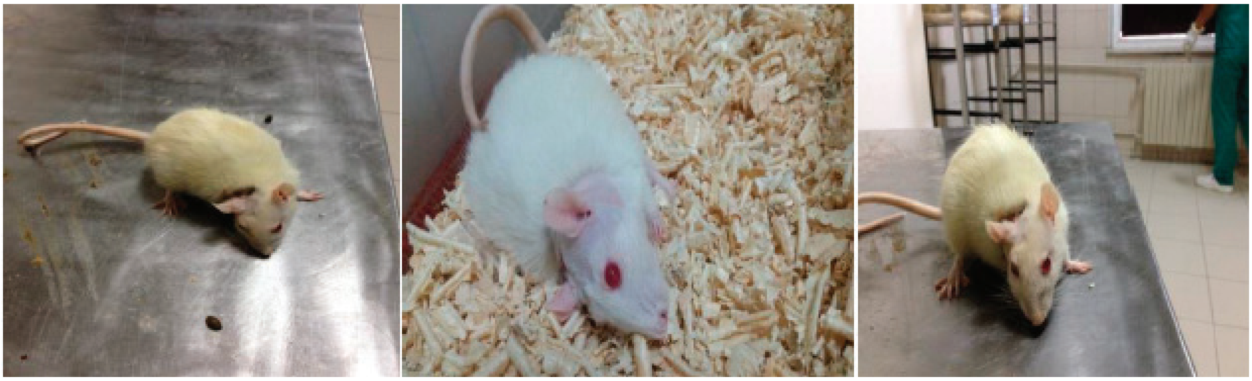

Figure 3a-d. Postoperative views (Behavioral asymmetries after unilateral labyrinthectomy: head tilting toward the operated side and limb extending on the intact side)

- Taking a lying position with leg support toward the side of the lesion was given 7 points.
- Turning in one direction or taking a lying position using the legs on the lesion side were given 6 points.
- Moving by using both legs was given 5 points.
- Wandering around while the head was rarely falling on the lesion side was given 4 points.
- Wandering around while the head was leaning on the lesion side was given 3 points.
- If the asymmetry was difficult to detect, 2 points were given.
- If the postural asymmetry was detectable only when the rat was lifted, 1 point was given.

Statistical Analysis

The data were analyzed using the IBM Statistical Package for the Social Sciences (SPSS) Version 23. The normality of the data was examined using the Shapiro Wilk test. Kruskal Wallis, Friedman test and Wilcoxon test were carried out to compare data that did not show normal distribution. The results were presented in the form of medians (minimum–maximum) and frequencies. The statistical significance level was set at $p<0.05$.

RESULTS

Nystagmus Values

Table 1 shows the change of the nystagmus values of the groups as per the day. There was no significant difference between EG and CG on days 1 and 2 in terms of the nystagmus values. However, there were statistically significant differences between EG and NCG and between CG and NCG ($p<0.001$). There was not any statistically significant difference between the groups in terms of the nystagmus values of the rats in each of the 3 groups whose nystagmus persisted on day 3 ($p=0.218$). Nystagmus values in EG and CG decreased over the days. The rate of decrease was statistically significant from day 1 to day 2 ($p<0.05$), but not significant from day 2 to day 3. In NCG, the decrease in nystagmus values was significantly different between all pairs of days ($p<0.05$). Nystagmus was observed in all rats in all 3 groups on days 1 and 2. On day 3, nystagmus persisted in 3 rats in EG, in 5 rats in CG and in 9 rats in NCG. On days 7 and 15, none of the rats were observed to have nystagmus. When the ratios in each time period were compared by carrying out a ratio test, there was a statistically significant difference between EG and NCG in terms of the number of rats whose nystagmus healed on day 3 ($p<0.05$), whereas there was no statistically significant difference between CG and NCG and between EG and CG ($p=0.141$, $p=0.65$, respectively).

Assessment of Degree of Head Tilt

As shown in Table 2, in the first 3 days, no full healing was observed in the degree of head tilt of any rat. There was no statistically significant difference between the groups in terms of the degree of head tilt on these days ($p=0.148$, $p=0.148$, $p=0.060$, respectively). On day 7, there was no statistically significant difference between the groups in terms of the

Table 1: The change of the nystagmus values of the groups based on the days

		1st Day	2nd Day	3rd Day	7th Day	15th Day
Group 1	Median (min-max)	6.5 (4-7)a	3.5(2-5)a	1 (1-2)	---	---
	N	10	10	9	---	---
Group 2	Median (min-max)	4 (3-5)b	1.5(1-2)b	1 (1-1)	---	---
	N	10	10	3	---	---
Group 3	Median (min-max)	4 (3-6)b	1.5(1-3)b	1 (1-1)	---	---
	N	10	10	5	---	---
	χ^2	16.6	16.3	3.0		
	P	<0.001	<0.001	0.218		

χ^2: Chi-Squared Test Statistics, a-c: no significant difference between groups with the same letter on the day

Table 2: The change of the degrees of head tilt values of the groups based on the days

		1st Day	2nd Day	3rd Day	7th Day	15th Day
Group 1	Median (min-max)	7(5-10)a	7(5-10)a	7 (5-7)a	5(5-7)b	5 (5-5)c
	N	10	10	10	9	6
Group 2	Median (min-max)	7 (5-7)a	7 (5-7)a	5 (5-7)ab	5(5-7)b	5 (5-5)ab
	N	10	10	10	5	3
Group 3	Median (min-max)	7 (5-10)a	7(5-10)a	6 (5-7)a	5(5-7)b	5 (5-5)ab
	N	10	10	10	6	4
	χ^2	3.8	3.8	5.6	1.6	0.0
	P	0.148	0.148	0.060	0.459	1.000

χ^2: Chi-Squared Test Statistics, a-c: no significant difference between groups with the same letter on the day

Table 3: The change of the postural deficit values of the groups based on the days

		1st Day	2nd Day	3rd Day	7th Day	15th Day
Group 1	Median (min-max)	7.5 (6-9)a	7 (5-9)a	5 (4-7)a	4 (3-5)a	2 (1-3)
	N	10	10	10	10	10
Group 2	Median (min-max)	5 (5-6)b	5 (4-6)b	3.5(3-4)b	2.5 (2-4)b	1 (1-3)
	N	10	10	10	10	10
Group 3	Median (min-max)	6 (5-8)b	5 (4-7)b	4 (3-6)b	3 (2-4)b	2 (1-2)
	N	10	10	10	10	10
	χ^2	14.8	1.9	15.2	12.7	5.9
	P	0.001	0.002	0.001	0.002	0.053

χ^2: Chi-Squared Test Statistics, a-c: no significant difference between groups with the same letter on the day

assessment of the rats whose heads were tilted more than normal (p=0.459). On day 15, there was no statistically significant difference in terms of the values of the rats whose heads were tilted more than normal (p=1). On day 7, the degree of head tilt became normal in 5 rats in EG, in 4 rats in CG, and in 1 rat in NCG. When the ratios in each time period were compared by carrying out a ratio test, there was no statistically significant difference between the groups in terms of degree of head tilt on day 7 (between EG and NCG, CG and NCG, EG and CG; p=0.141, p=0.3, p=1, respectively). On day 15, the degree of head tilt became normal in 7 rats in EG, 6 rats in CG, and 4 rats in NCG. When the ratios in each time period were compared by carrying out a ratio test, there was no statistically significant difference between the groups in terms of degrees of head tilt on day 15 (between EG and NCG, CG and NCG, EG and CG; p=0.37, p=0.65, p=1, respectively).

Postural Deficit Values

As shown in Table 3, there were no rats who fully recovered in terms of postural deficit values during the 5 different days when the measurements were made in any group. There was a statistically significant difference between postural deficit values obtained over time when each group was assessed in itself ($p<0.05$). The values obtained on each different day in each group were different from each other. Postural deficit values gradually dropped from day 1 to day 15 over time. And these drops were statistically significant ($p<0.05$). In conclusion, observation of the postural deficit values after labyrinthectomy showed that the rates of healing in EG and CG were similar to each other on days 1, 2, 3, and 7, but were statistically significantly better than those in NCG (p=0.001, p=0.002, p=0.001, p=0.002, respectively). No statistically significant difference was detected between the groups on day 15 (p=0.053).

DISCUSSION

Meniere's disease, trauma, prolonged vestibular neuritis, labyrinthitis, vascular causes, autoimmune inner ear disease and benign paroxysmal vertigo are among the causes of unilateral vestibular dysfunction. Primarily, treatment methods covering all kinds of pharmacological and compensation programs are administered in peripheral vestibular diseases. However, surgical options may be on the agenda for solving the problem in patients for whom these treatment methods are insufficient and who have become unable to do their job due to vertigo attacks and have reached the point of being detached from life (3).

Labyrinthectomy is quite an effective ablative surgical method of intervention that can be administered for vertigo control in unilateral peripheral vestibular pathologies where medical treatment has failed and there is a significant hearing loss (1).

Total hearing loss is an expected result after labyrinthectomy, which limits the scope of application to patients with preoperative severe hearing loss (15).

A significant imbalance develops in firing rates of vestibular nuclei, with a significant portion of ipsilateral second-order neurons going into silence after unilateral vestibular function losses due to causes such as labyrinthectomy, but such an imbalance heals over time (16).

In two different studies, it was observed that static imbalance in guinea pigs healed in the first week and in Rhesus monkeys in the third week (17, 18).

Part of the healing in the rest activity of second-order neurons is intrinsic. On the other hand, other subsequent lesions in other parts of the central nervous system (CNS), such as spinal cord or inferior olive, can cause temporary insufficiencies and a recurrence of static imbalance symptoms. Two important results can be inferred from these observations. The first of them is that a surprising compensation can occur for static vestibular pathologies. However, it might take a few weeks. The second one is that this compensation may be disrupted by other changes in the CNS in subsequent periods and lead to a recurrence of symptoms due to static vestibular imbalance. After permanent unilateral vestibular function losses, asymmetry in dynamic responses to head movements continues for a long time even if the imbalance heals (16).

After a unilateral labyrinthectomy, oculomotor and postural symptoms appear, such as spontaneous nystagmus, the deviation of the head and body toward the side undergoing surgery, and abnormal amplitude and timing in vestibulo-ocular and vestibulospinal reflexes (19, 20). Most of such symptoms disappear within days or weeks based on vestibular compensation. Certain drugs positively influence the vestibular compensation process that develops after labyrinthectomy, and certain others negatively (21).

N-acetyl-DL-leucine (Tanganil) has long been successfully used in the treatment of acute vertigo (22, 23). Günther et al. used D and L forms of enantiomers of N-acetyl-DL-leucine (Tanganil), which have been used for treating acute vertigo for many years to improve postural compensation after vestibular neurectomy and labyrinthectomy, on rats in their study (14). They rated nystagmus, postural asymmetry and the degree of deviation of the head, which are some of the behavioral tests, before labyrinthectomy and on days 1, 3, 7, and 15 after labyrinthectomy. They observed that nystagmus disappeared on day 3 and that the deviation of the head and postural asymmetry continued until day 15. They did not observe any significant differences between the enantiomers of N-acetyl-DL-leucine (Tanganil) in terms of efficacy.

We also based our study on the study by Günther et al. (14) and chose to observe nystagmus, the degree of head tilt and postural asymmetry on days 1, 2, 3, 7, and 15 as the behavioral signs of vestibular imbalance after labyrinthectomy. In our study, we chose to work on rats as the experimental model because of the facts that rats are easy to look after, they breed fast, they can be obtained in large numbers for acceptable statistical results, experimental procedures with rats are easy, rats and humans have similar overall and ear anatomy, and it is easy to operate on rats.

Park et al. (24) examined the restoration of vestibular functions after a unilateral labyrinthectomy on rats. In their study, nitric oxide, which has antioxidant effects, was used to form two groups: rats that were and that were not given nitric oxide synthase inhibitor. They observed that nystagmus disappeared on day 7 in the group that was given nitric oxide synthase inhibitor, whereas it took 3 days for nystagmus to disappear in the group that was not given any drugs. The study of Park et al. supported our idea of using CoQ10, which is a powerful antioxidant, as an alternative to other treatments because of its antioxidant effect following a labyrinthectomy.

CoQ10 has a lipophilic characteristic, hence is insoluble in water due to its long side ring made up of 10 isoprenoids. For this reason, for the absorption of CoQ10, which is taken exogenously, it is necessary for it to be transported by chylomicrons to lymph and peripheral blood tissue. Because there is no intravenous form of it for humans yet, studies have been conducted for oral forms of it. Substances such as soybean oil, olive oil, and corn oil benefit CoQ10 absorption due to its hydrophobic characteristic (25). Such preparations, of which gastrointestinal absorption is about 4–6%, can be effective if they are taken at high doses and for a long time (26). Studies on volunteering subjects have demonstrated that CoQ10 has no side effects even after its oral intake at high doses (3000 mg/day), revealing that it is an agent that can be used safely (27). The injectable form of CoQ10 has been administered in the form of acute treatment in most of the studies carried out. When CoQ10 is administered parenterally, almost all of it is absorbed, and it reaches stable concentration in serum on the 6th day (26). The amount of CoQ10 detected in serum when it is given orally once a day at a dose of 150 mg/kg is equal to the amount of it measured when given intraperitoneally at a dose of 10 mg/kg. As parenteral CoQ10 absorption is close to 100%, the parenteral route was chosen in our study as the route of injection. CoQ10 was given at a dose of 10 mg/kg once a day, for 3 days before the operation and 3 days after the operation.

Khan et al. (9) examined patients with complaints of tinnitus who were found to have a low level of plasma CoQ10 prior to treatment. They found that 3×100 mg of CoQ10 supplementation per day reduced the patients' tinnitus complaints. Fetoni et al. (10) carried out a study on guinea pigs and observed that CoQ10 treatment inhibited free radicals induced by gentamicin, an ototoxic agent, and that it preserved hair cells against gentamicin ototoxicity and reduced gentamicin-induced hearing loss. In another study, Fetoni et al. (11) investigated the effectiveness of systemic and transtympanic administration of CoQ10 treatment for sudden hearing loss due to noise and assigned some rats into two groups. They systematically administered 100 mg/kg of CoQ10 to a group for 4 days after acoustic trauma and transtympanically administered CoQ10 to another group at 20–40% concentration 1 hour before acoustic trauma. They examined treatment responses through ABR on days 1, 3, 7, and 21. They found that CoQ10 was effective against sudden hearing loss due to noise and that its transtympanic and systemic administrations had similar results. They concluded that in sudden hearing losses, CoQ10 can be administered transtympanically, which is a minimally invasive procedure.

Kumar et al. (12) have found that in vertigo and Meniere-like syndromes, CoQ10 supplementation — which reduces proinflammatory cytokines and blood viscosity, eliminates free radicals and has a vasodilator effect — stimulates the immune system and corrects symptoms in patients with low CoQ10 concentration.

In this study, we assessed the effect of parenteral use of CoQ10 on the vestibular compensation process after labyrinthectomy. A review of the literature showed that there were numerous studies on the treatment of vestibular compensation after labyrinthectomy, but no study involving the use of CoQ10. Based on our study, the analysis of the effects of CoQ10 use after labyrinthectomy on the degree of head tilt revealed that it made positive contributions to the compensation process in EG and CG compared to NCG, but there was no statistically significant difference between the groups. When the postural deficit values were examined, statistically significant differences were found between all pairs of groups on days 1, 2, 3, and 7, but not on day 15. When the nystagmus values were examined, statistically significant differences were found between the pairs of groups on days 1 and 2, but not on day 3. The rate of healing in EG and CG was better than that in NCG on all three days, and the rates of healing in EG and CG were found to be similar. According to the assessment based on degrees of head tilt, postural deficit values and nystagmus, the results of EG and CG were found to be close to each other. We think this result may have been due to the weak antioxidant effect of soybean oil.

The values of EG and CG were somewhat higher than those of NCG in terms of the degree of head tilt, but there was no statistically significant difference among the three groups. Although EG and CG were found to differ statistically significantly from NCG on certain days in terms of postural deficit values and nystagmus, this significance remained limited to those days. We think that the fact that in our study, the effect of CoQ10 on the vestibular compensation process was limited may be due to its limited dose, short duration of administration, and the limited number of rats. We believe that the effects of CoQ10 on the vestibular compensation process after labyrinthectomy should not be neglected. Despite the fact that we administered it at limited doses for a short term on a limited number of rats, CoQ10 should be used in larger samples, in higher doses, and for a longer time because CoQ10 has positive, though limited effects, on the vestibular compensation process.

Main Points

- Labyrinthectomy is a treatment method of last resort for controlling vertigo.
- After a unilateral labyrinthectomy, oculomotor and postural symptoms appear, such as spontaneous nystagmus, the deviation of the head and body toward the side undergoing surgery, and abnormal amplitude and timing in vestibulo-ocular and vestibulospinal reflexes.
- CoQ10, which is a powerful antioxidant, can be used as an alternative to other treatments because of its antioxidant effect following a labyrinthectomy.
- We assessed the effect of parenteral use of CoQ10 on the vestibular compensation process after labyrinthectomy. We believe that CoQ10 has positive, though limited effects, on the vestibular compensation process.

Ethics Committee Approval: This study was conducted with 1. Ondokuz Mayıs University Faculty of Medicine ethics committee approval (2016/16).

Informed Consent: Written informed consent was obtained.

Peer-Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- F.T., S.G.E., M.E.G.; Data Acquisition- F.T., S.G.E., M.E.G.; Data Analysis/Interpretation- F.T., S.G.E., M.S.Y.; Drafting Manuscript- F.T., S.G.E., M.G.; Critical Revision of Manuscript- F.T., S.G.E., M.G., M.S.Y.; Final Approval and Accountability- F.T., S.G.E., M.S.Y., M.E.G., M.G.

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