The Journal of International Advanced Otology

J Int Adv Otol 2016; 12(3): 303-9 • DOI: 10.5152/iao.2016.1166

Original Article

Efficacy of Cortexin and Methylprednisolone on Traumatic Facial Nerve Paralysis

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OBJECTIVE: The aim was to investigate the efficacy of cortexin and methylprednisolone on recovery in cases of traumatic facial nerve paralysis occurring after facial nerve trauma.

MATERIALS and METHODS: The study was performed on 21 healthy rabbits. The buccal branches of the left facial nerves of all the rabbits were pressed, and facial nerve paralysis occurred. The rabbits were randomly divided into three equal groups: 3 mg/day cortexin intramuscularly, 1 mg/kg/day methylprednisolone intramuscularly, and 3 mg/day saline intramuscularly were administered for 10 days in Group I (cortexin group), Group II (methylprednisolone group), and Group III (control group), respectively. Electromyography was performed on the 7th, 14th, and 21st days to evaluate their improvement. Following this, the traumatic buccal branches of the facial nerves of rabbits were extracted and subjected to histopathological examination.

RESULTS: There was a significant difference between the cortexin and methylprednisolone groups and the control group in terms of neural fibrotic degeneration, myelin degeneration, axonal degeneration, normal myelin production, and edema. When the cortexin and methylprednisolone groups were compared with each other, there was no significant difference between them, except for an increase in collagen fibers. Cortexin significantly reduced the collagen fiber increase to a greater extent than methylprednisolone. The electromyography findings did not show any significant difference between the groups or within the groups.

CONCLUSION: Our study suggests that cortexin and methylprednisolone are effective for healing traumatic facial nerve paralysis with intact nerve integrity; however, cortexin is unable to cause significant improvement, which is superior to that caused by methylprednisolone.

KEYWORDS: Facial nerve paralysis, cortexin, methylprednisolone, electromyography

INTRODUCTION

The facial nerve (FN), which provides all the innervations of the mimic muscles of the face, has a functionally mixed structure. The symmetry of the right and left half of the face during movements or at rest is very important for esthetics. Psychological problems may occur when the symmetric structure between both sides is disrupted because of FN function loss and when the mimic muscles of the face cannot fulfill this function [1].

Trauma is the second most common cause of FN paralysis [2, 3]. Trauma-induced peripheral FN paralysis is particularly seen after face and temporal bone trauma. More rarely, it may occur as a result of birth trauma or iatrogenic reasons [4]. Iatrogenic FN injury can often occur during tympanomastoid surgery, vestibular nerve or endolymphatic sac surgery, parotid surgery, pontocerebellar angle tumor surgery, and surgery for chronic otitis media [5].

Various agents are used in the medical treatment of traumatic FN paralysis (TFNP). Corticosteroids (CS) are used in the treatment of TFNP; however, their efficacy has not yet been fully demonstrated [6]. Cortexin has entered clinical use since 1999 for the treatment of various diseases. It is a molecule with a GABAergic effect and shows its effects by regulating the excitatory and inhibitory amino acid balance as well as serotonin and dopamine levels [7-10].

The aim of this study was to investigate the efficacy of cortexin and methylprednisolone in the treatment of TFNP caused by trauma.

Presented in: This study was presented at the 36th Turkish Otolaryngology and Head and Neck Surgery Congress, 5-9 November 2014, Antalya, Turkey.

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Submitted: 18.04.2015 **Revision received:** 07.01.2016 **Accepted:** 27.05.2016

MATERIALS and METHODS

The study was carried out on 21 healthy New Zealand white rabbits weighing 1400–3000 grams based on the approval of Fırat University Ethics Committee. The supplies were used in this study were provided by the unit of Fırat University Scientific Research Projects (FUSRP). All the rabbits were evaluated in terms of FN function (symmetric mustache movements during chewing and the existence of blink reflex when compressed air is applied), and the rabbits with normal FN assessment were included in the study.

A maximum of three rabbits were placed in each cage at Fırat University Experimenta Research Center, and were fed in a standard manner with a mechanism whereby they could reach unlimited special bait and water.

The same surgical procedure was applied by the same surgeon on all the rabbits included in the study. All the rabbits included in the study were anesthetized with 10 mg/kg xylazine hydrochloride (Rompun; Bayer AG, Leverkusen, Germany) and 50 mg/kg ketamine hydrochloride (Ketalar*; Eczacıbaşı Pharmaceuticals, İstanbul, Turkey) given intramuscularly, and the skin of the rabbits were shaved from the corresponding regions to FN trace and dried and cleaned with 0% ethanol and povidone–iodine. The procedure was performed with an operating microscope (Olympus BX51; Tokyo, Japan) under sterile conditions. A horizontal incision about 2 cm long was made parallel to the mandible below the eyes of the rabbits; skin and the subcutaneous tissues were dissected until the superficial fascia was reached, then the microscopic dissection was performed and the buccal branch of the FN was identified by the help of a nerve stimulator. Then, the buccal branch of the FN was compressed and crushed for one minute with a Yaşargil–Phynox aneurysm clip (Aesculap AG; Tuttlingen, Germany) with a closing pressure of 188 g/cm^2 and a tolerance pressure of 162 to 198 g/cm^2 (Figure 1). The muscle layer of the pressed region of the facial buccal branch was marked with 5.0 polyropylene (Prolene; Ethicon, Cincinnati, Ohio, USA) in order to recognize it. After completing the procedure, the skin was closed with 4.0 silk (Silk; Ethicon, Cincinnati, Ohio, USA). A prophylactic of 20–40 mg/kg cefazolin sodium (Cefazolin flake; Mustafa Nevzat İlaç San, İstanbul, Turkey) was applied in the IM route one hour before and after the surgery. After surgical procedures, the rabbits were divided into three equal groups, randomly including seven rabbits per group, and followed up for 21 days.

Group I (cortexin group): 3 mg/day single dose IM cortexin (Koptekcnh; Geropharm pharmaceutical company, Saint Petersburg, Russia) was administered for 10 days after the FN crush injury was created.

Group II (methylprednisolone group): 1 mg/kg/day single dose IM methylprednisolone (Prednol-L; Mustafa Nevzat İlaç San, İstanbul, Turkey) was administered for 10 days after the FN crush injury was created.

Group III (control group): 3 mg/day single dose IM saline was administered for 10 days after the FN crush injury was created.

Preparation of the Surgical Specimens

All the subjects included in the study were anesthetized with 10 mg/kg xylazine hydrochloride and 50 mg/kg ketamine hydrochloride given intramuscularly on the 22nd day, and the previous incision site was used in order to reach the FN buccal branch, which was marked with 5.0 Prolene during the initial surgical procedure. The FN buccal branch was cut from 5 mm proximal and 5 mm distal of the traumatic part. The extracted specimens were fixed in 10% glutaraldehyde. Then, the specimens were kept in 1% osmium tetraoxide for 30 minutes and dehydrated in ethanol incrementally and placed in Epon.

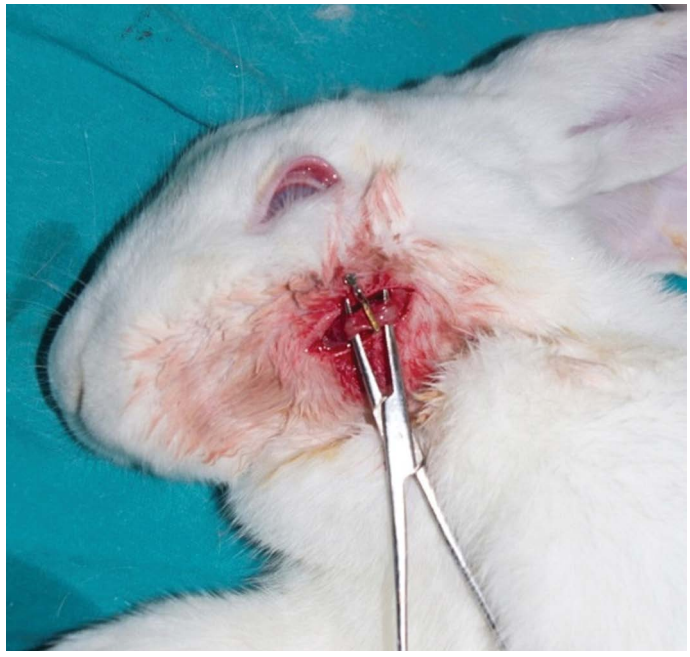

Figure 1. Creating pressure with a Yaşargil–Phynox aneurysm clip on the buccal branch of the facial nerve.

Sections parallel and perpendicular to the nerve at a thickness of 1.5 microns were obtained with Ultratome III blades (Shandon Finesse, Thermo Fisher Scientific Inc, England). Mason trichrome and hematoxylin and eosin (H&E) Stained sections were evaluated by the same expert pathologist with a light microscope with x40, 100, 200, and 1000 magnification.

Evaluation of the Surgical Specimens

On the stained sections, neural fibrotic degeneration, an increase in collagen fibers, myelin degeneration, axonal degeneration, Schwann cell proliferation, normal myelin production, and edema were evaluated as follows: Not present: - (0), mild: + (1), moderate: ++ (2), or severe: +++ (3). Eyepiece graticules (in a 1x1 mm 100 equally checkered ocular micrometer) attached to the Olympus light microscope were used for observation, and four sections belonging to each specimen (by ×40, 100, 200, 1000 objective magnification) were evaluated, and the average score was used as the final score.

EMG Application for the Subjects

Electromyography (EMG) was performed for all the rabbits on the 7th, 14th, and 21st days. During the application of EMG, needle electrodes were placed on the buccal muscles of the rabbit and stimulus was given to the main trunk of the FN in order to measure the action potentials and latent periods formed in the buccal branch. The obtained data were transferred to the computer (Figure 2, 3).

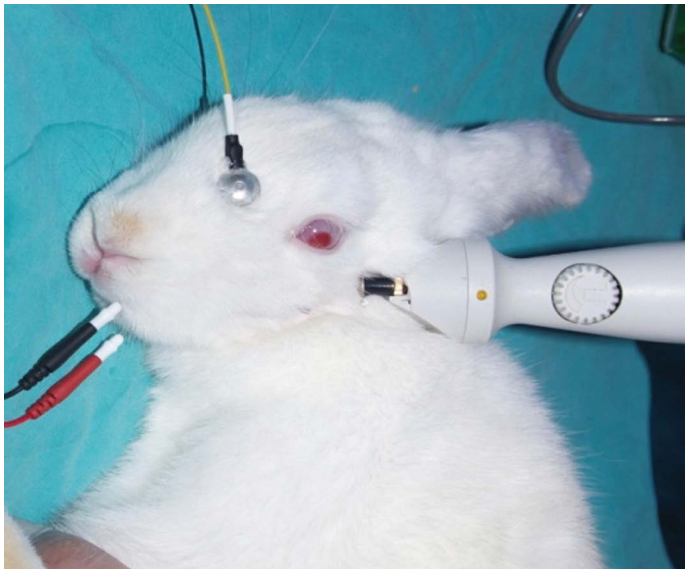

Figure 2. EMG application on rabbits on the 7th, 14th, and 21st days.
EMG: electromyography

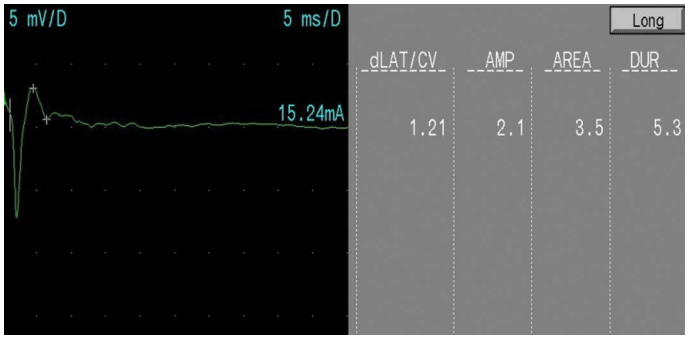

Figure 3. EMG data example.
EMG: electromyography

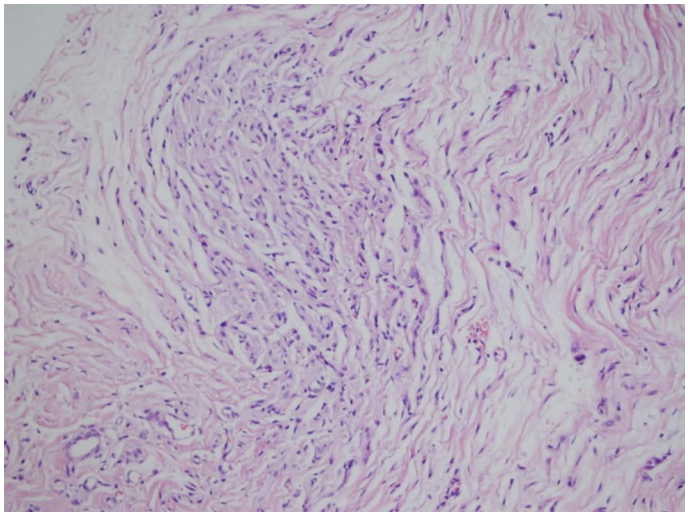

Figure 4. Neural fibrotic degeneration in Group III (hematoxylin and eosin, ×200).

Statistical Analysis

Statistical analysis of the resulting EMG data and the histopathological data was performed using the IBM SPSS 21.0 software program (IBM Corp.; Armonk, New York, USA). One-way analysis of variance was used to compare the evaluation of amplitude and the latency

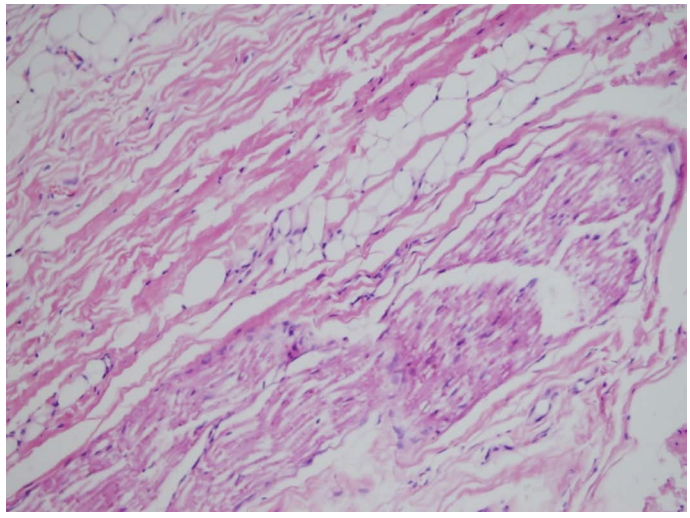

Figure 5. Increase in collagen fibers in Group II (hematoxylin and eosin, ×200).

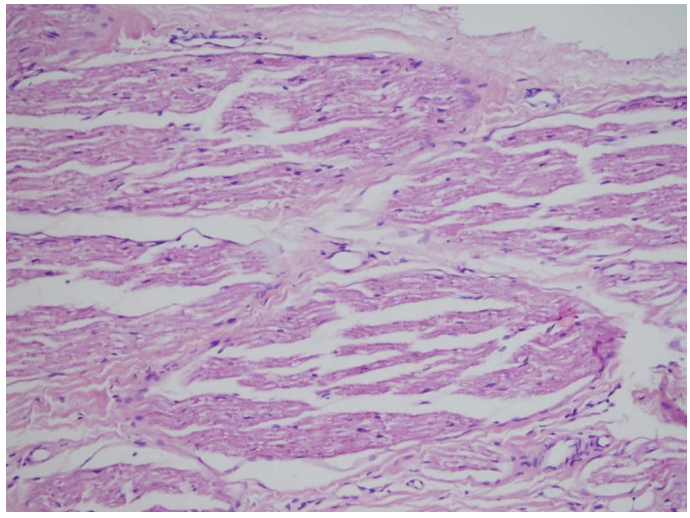

Figure 6. Myelin degeneration in Group III (hematoxylin and eosin, ×200).

of the groups. Dunnett's test was used to determine the differences between groups as a post-hoc test. The analysis of variance was used for evaluation of measurements within the groups (1 week, 2 weeks, 3 weeks) in the repeat measures. The chi-square test was used in the analysis of the qualitative data (pathology results). A value of $p<0.05$ was considered statistically significant.

RESULTS

Histopathologic scores of the groups are given in Table 1.

Neural fibrotic degeneration was greatest in Group III, followed by in Group I and Group II, and was statistically significant between Groups III and II ($p<0.05$) (Table 2, Figure 4).

The increase in collagen fibers was greatest in Group III among the groups. This was followed by Group I and Group II, respectively. There was a statistical significance between Group III and the other groups ($p <0.05$). There was no statistical significant difference between Groups I and II (Table 2, Figure 5).

Myelin degeneration was the least in Group I. This was followed by Group II and then Group III, respectively. There was a statistical

Table 1. Histopathological findings of traumatic facial nerve paralysis in all the groups

Groups	Number of subjects	Neural fibrotic degeneration	Increase in collagen fibers	Myelin degeneration	Axonal degeneration	Schwann cell proliferation	Normal myelin production	Edema
I (Cortexin)	1	+	++	+	++	++	++	+
	2	+	++	-	+	+	+++	+
	3	+	++	+	+	+	++	+
	4	-	++	++	+	+	++	+
	5	+	+	+	-	++	++	++
	6	+	++	+	+	++	+++	+
	7	+	+	-	-	+	+++	-
II (Methylprednisolone)	1	++	++	+	+	+	++	+
	2	++	++	++	++	++	++	++
	3	+++	+++	++	+	+	++	++
	4	+	++	+	++	+	++	+
	5	++	++	+	+	++	++	++
	6	+++	++	+	-	+	+++	++
	7	+	+	-	+	++	+++	+++
III (Saline)	1	+++	+++	+++	+++	+	+	++
	2	+++	+++	+++	++	-	+	+++
	3	+++	+++	++	+++	++	+	+++
	4	+++	++	+++	++	+	+	++
	5	++	++	+	++	-	++	+++
	6	+++	+	+++	+++	+	++	+++
	7	+++	++	+++	+++	-	+	++

Evaluated as follows: Not present: - (0); mild: + (1); moderate: ++ (2); severe: +++ (3)

Table 2. Statistical comparison of the groups in terms of histopathological parameters

	p values of the compared groups		
Histopathological parameters	**I–III**	**I–II**	**II–III**
Neural fibrotic degeneration	0.0029	0.0821	0.0460
Increase in collagen fibers	0.1471	0.4724	0.5134
Myelin degeneration	0.0321	0.0907	0.3430
Axonal degeneration	0.0117	0.0267	0.7165
Schwann cell proliferation	0.1260	0.1260	0.5892
Normal myelin production	0.0131	0.0159	1.0000
Edema	0.0117	0.1393	0.1656

p<0.05 is statistically significant

significant difference between Group I and Group III (p<0.05), but there was no significant difference between the other groups (Table 2, Figure 6).

Axonal degeneration was greatest in Group III. This was followed by Group II and Group I, respectively. There was a statistical significant difference between Group III and the other groups (p<0.05), but there was no significant difference between Groups I and II (Table 2, Figure 7).

When the groups were evaluated according to the proliferation of Schwann cells, Schwann cell proliferation was also observed to be similar in Group I and Group II. Schwann cell proliferation was the least in the control group. There was no statistical significant difference when the groups were compared to each other (Table 2).

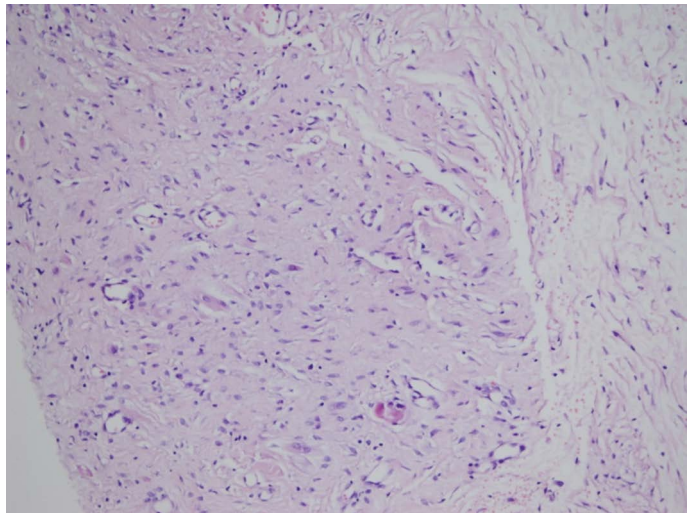

Figure 7. Axonal degeneration in Group III (hematoxylin and eosin, ×200).

Normal myelin production was the least in Group III, followed by Group II. Myelin production was greatest in Group I. When Group III was compared to the other groups, a statistically significant difference was found (p<0.05). There was no statistical significance between Groups I and II (Table 2, Figure 8).

Table 3. Mean values of the latent period and amplitude of groups in electromyography (EMG)

	Mean values of the latent period			Mean value of the amplitude		
Groups	**1st week**	**2nd week**	**3rd week**	**1st week**	**2nd week**	**3rd week**
I (n=7)	5.10 ±0.65	6.34±0.48	6.15±0.42	3.92±0.50	4.47±0.49	4.24±0.59
II (n=7)	5.37±0.59	6.20±0.56	6.37±0.96	4.67±0.85	5.08±0.69	5.20±0.95
III (n=7)	5.48±0.39	6.10±0.33	6.15±0.04	6.01±0.43	3.47±0.42	4.25±0.55

EMG: electromyography

Table 4. Comparison of the control group and other groups by Dunnett's t-test

	p value of the latent period			p value of the amplitude		
Groups	**1st week**	**2nd week**	**3rd week**	**1st week**	**2nd week**	**3rd week**
I–III	0.84	0.90	1.00	0.06	0.35	1.00
I–II	0.25	0.25	0.36	0.75	0.75	0.95
II–III	0.98	0.98	0.95	0.24	0.09	0.57

$p<0.05$ is statistically significant

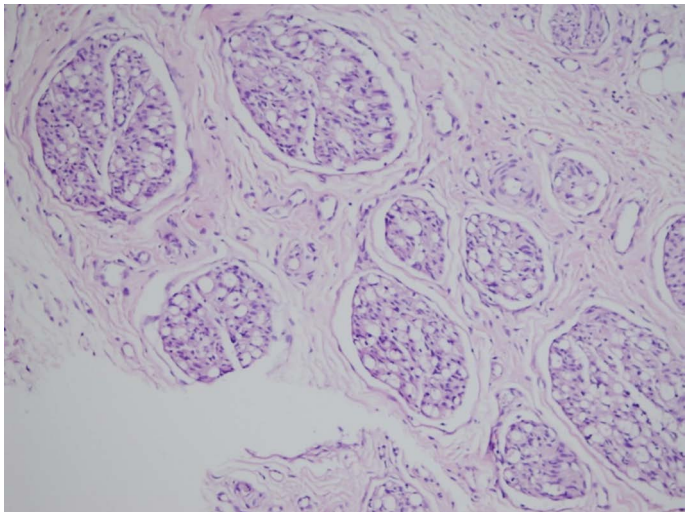

Figure 8. Normal myelin production in Group II (Masson's trichrome, ×200).

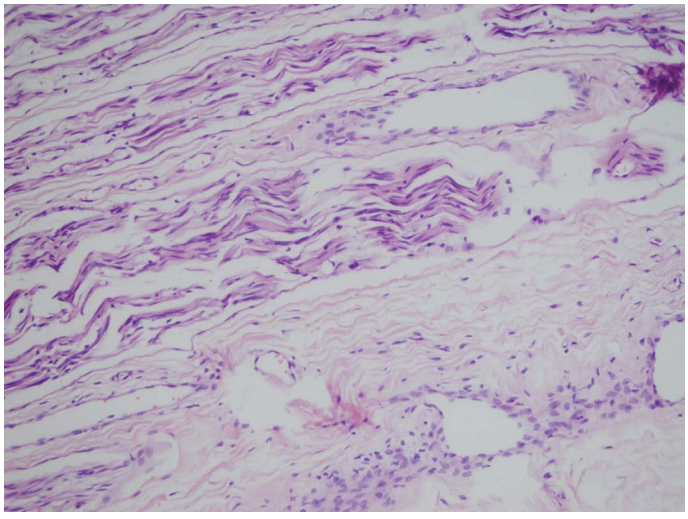

Figure 9. Edema in Group II (hematoxylin and eosin, ×200).

The least edema was seen in Group I among the groups, followed by Group II. The greatest edema was observed in the control group. This showed statistical significance between Group I and Group III ($p<0.05$) (Table 2, Figure 9).

The groups did not show any statistical difference according to the results of the EMG applied at the first, second, and third weeks (Table 3, 4).

DISCUSSION

Loss of FN function due to various causes is called facial paralysis. Many factors such as trauma, infection, inflammation, tumoral structures, and iatrogenic causes play a role in the etiology of facial paralysis [11]. FN is among the motor cranial nerve pairs in which loss of function develops most frequently. This is because FN shows a meandering course compared with other cranial nerves in the fallopian canal, which is a long, narrow canal [12]. A large portion of peripheral FN paralysis, as much as 90%, develops depending on the pathologies in these channels [13, 14].

After peripheral FN paralysis (PFNP), severe functional and social problems such as difficulty in communicating with other individuals depending on the disability to use the facial expression muscles, synkinesia (not to be able to close the eyelids exactly), and speech disorders may occur in patients. Therefore, in PFNP rehabilitation, physicians, patients, and relatives of patients should have a good relationship with each other. Furthermore, patients and their relatives should be informed about the treatment, future procedures, and possible complications [15].

Bell's palsy is the most common PFNP. It is considered to be an idiopathic mononeuropathy. Although the etiology of Bell's palsy is not entirely clear, microcirculation disorders, ischemic polyneuropathy, viral infections, and autoimmune reactions are considered as causes [16]. At present, trauma is the second major cause of PFNP. Temporal bone fractures, iatrogenic trauma (surgery), penetrating injuries of the face, and gunshot wounds may cause PFNP [2, 3].

Up to the present from the past, many agents have been used to cure periphery nerve damage and research has continued to find more effective treatments. Today, steroids are the agents most commonly used in the treatment of PFNP. CS reduce the inflammatory response in tissue and facilitate the formation of the healing response with potent anti-inflammatory effects [17]. Austin et al. [18] reported that the use of steroids in the treatment of Bell's palsy was superior compared

to a placebo. Likewise, Sullivan et al. [19] found that prednisolone used in the early period of the treatment of Bell's palsy increased the healing significantly. Xia et al. [20] reported that a combination of prednisolone with acupuncture was a more effective treatment for Bell's palsy.

Sekiya et al. [21] defended that cochlear neuron damage could be prevented due to the use of methylprednisolone in cases of cochlear nerve degeneration occurring as a result of compression; this was attributed to the anti-edema effect of CS. Lieberman et al. [22] used CS in the treatment of FN paralysis damage as a result of compression and reported that CS were effective in restoring the function of the FN. However, Karlidag et al. [23] investigated the effects of methylprednisolone and n-acetyl cysteine in the treatment of TFNP and reported that methylprednisolone did not cause increased regeneration in the cases where the FN was totally cut and sutured together again. Similarly, Nguyen et al. [24] investigated the efficacy of CS in the early period of iatrogenic wound healing, and reported that CS could reduce the number of leukocytes in surgical sites by 50%. In our study, maximum edema occurred in the control group. Methylprednisolone increased Schwann cell proliferation, collagen, and myelin production, and reduced axonal degeneration, thus it was effective in the treatment of TFNP.

It has been reported that in ischemic, hemorrhagic, and stroke cases, cortexin causes a decrease in neurological symptoms after the fifth day, and if the treatment was started as soon as possible, a neuroprotective effect was more evident [8]. It has been shown in another study that the use of cortexin accelerated the recovery in patients with ischemic cerebrovascular events and severe head trauma [9]. Normalization of the trigeminal nerve neurophysiology has been reported depending on the use of cortexin in the neuroprotective treatment for patients with periodontal disease; furthermore, inflammatory processes were reported to have improved more quickly, recovery was 1.5–2 times faster in chronic periodontal disease after the application of cortexin, and the remission duration was observed to be prolonged [10]. In another study, cortexin was reported to provide an increase in volume of the atrophic optic nerve in patients with optic neuritis that had developed due to multiple sclerosis [25]. To the best of our knowledge, this is the first study in the literature investigating the effects of cortexin in the treatment of TFNP. According to our EMG results, there was no significant difference between the groups, but the histopathology revealed significant results. In the histopathological evaluation, significant differences were identified between the cortexin and control groups in terms of neural fibrotic degeneration, increase in collagen fibers, myelin degeneration, axonal degeneration, Schwann cell proliferation, normal myelin production, and edema. When we compared methylprednisolone with cortexin, axonal degeneration and normal myelin production were the statistically significant differences.

In conclusion, according to the present study, cortexin and methylprednisolone used for the treatment of TFNP are more effective than a placebo, but cortexin is not superior to methylprednisolone. Our study is important as it is the only study in the literature showing the efficacy of cortexin in the treatment of TFNP. However, randomized controlled studies are needed to fully state the clinical use of cortexin in the treatment of TFNP.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Fırat University.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - T.T., İ.K.; Design - E.K.; Supervision - Ş.Y., T.K.; Resources - T.T.; Materials - C.F.D., M.M.A.; Data Collection and/or Processing - T.T., İ.K.; Analysis and/or Interpretation - T.T., C.F.D., M.M.A.; Literature Search - T.T., İ.K.; Writing Manuscript - T.T., İ.K.; Critical Review - Ş.Y., E.K.

Acknowledgements: We thank to Fırat University Scientific Research Projects (FUSRP) for financial support.

Conflict of Interest: No conflict of interest was decared by the authors.

Financial Disclosure: This study was funded by Fırat University Scientific Research Projects.

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