DOI: https://doi.org/10.53555/nnmhs.v9i8.1783 Publication URL: https://nnpub.org/index.php/MHS/article/view/1783

THE EFFICACY OF CORTICOSTEROID AFTER FACIAL NERVE NEURORRHAPHY: A SYSTEMATIC REVIEW

Desnita Monica*

**Faculty of Medicine, Indonesian Islamic University, Indonesia*

Corresponding Author:
Desnitamonica@ymail.com

Abstract

Background: *In case of comple transection of facial nerve, it is unclear whether or not corticosteroids will be beneficial after facial nerve neurorrhaphy.*

Aim: *The purpose of this systematic review was to determine whether or not corticosteroids are effective in promoting facial nerve regeneration and functional recovery following complete transection and neurorrhaphy.*

Methods: *Randomized controlled trials on human and animal models from Ovid MEDLINE and Ovid EMBASE that studied the efficacy of corticosteroids in total facial nerve damage followed by neurorrhaphy. Electrophysiology, histology, and functional recovery were the methods that were used to evaluate the results. On the other hand, there was no randomised controlled experiment carried out on humans. In a clinical context, it's possible that it won't be possible to conduct human trials that involve histology.*

Results: *Six animal investigations with a total of 248 participants met the inclusion criteria. Electrophysiological results revealed no differences between systemic corticosteroids and controls in terms of latency and amplitude. The results of a comparison between topical corticosteroid and the control group revealed no differences in latency and amplitude. In histologic outcomes, there were no differences in axon diameter between the systemic corticosteroid and control groups; however, the control group had thicker myelin. Comparing systemic corticosteroid to a placebo in terms of eye blinking, the results favoured the placebo.*

Conclusion: *When analysing electrophysiologic and functional recovery outcomes in animal models, this study did not demonstrate any possible benefits of systemic or topical corticosteroid administrations after facial nerve neurorrhaphy in complete transection.*

Keywords: *Corticosteroid; Facial nerve neurorrhaphy; Complete facial nerve transection; Nerve regeneration; Functional recovery.*

INTRODUCTION

The facial nerve consists of motor, sensory, and parasympathetic nerve fibres. By its anatomical location, it can be divided into intracranial, intratemporal, and extratemporal portions, with the more distal portion containing more motor fibres.1 Multiple aetiologies, including traumatic facial nerve injury, iatrogenic injury during parotid, soft tissue, orthognathic, or otologic surgery, and oncologic control surgery for head-and-neck cancer, can cause complete axonal disruption of the facial nerve.[1] Total facial nerve paralysis may result in facial asymmetry, corneal ulcer, inability to elevate the forehead, midface ptosis, and an unnatural or inability to grin, which may cause morbidity in the patient.[2]

After nerve injury, the distal peripheral nerve site undergoes an inflammatory response with macrophage function, followed by Wallerian degeneration and demyelination. The nerve regeneration procedure then commences.[3] Remyelination, axonal sprouting, and axonal regeneration constitute the molecular mechanisms of peripheral nerve repair.[4] Schwann cells begin to divide and proliferate following an injury. In the final stage, the axons penetrate the distal stump's endoneurial tube.[3] Neuroinflammation is the primary process following nerve injury; consequently, corticosteroids, which reduce perineural inflammation in numerous diseases, are utilised in facial nerve injury.

Corticosteroids reduce neural edoema and perineural inflammation, protect cells from peroxidation, prevent motor neuron mortality, slow the rate of anterograde degeneration, and promote recovery following nerve injury.[5–8] In cases of partial facial nerve injury, corticosteroid has been shown to enhance facial nerve regeneration and recovery rate.[9–11] Therefore, clinical trials and guidelines prescribe corticosteroids in high doses for partial facial nerve injury.[9] For the greatest functional outcome, the gold standard treatment for complete nerve injury is an immediate tension-free neurorrhaphy with end-to-end anastomosis or nerve interposition graft.[12] However, functional recovery does not reach the level before the injury. After facial nerve coaptation, adjunct corticosteroid therapy is proposed and prescribed in general clinical settings. However, the clinical utility of corticosteroids is questionable, and there is insufficient evidence to support their use. Moreover, corticosteroid use is not without its dangers. There have been reports of adverse effects including gastrointestinal distress, elevated blood glucose levels, elevated blood pressure, and psychotic episodes. Therefore, corticosteroid use should be studied to corroborate its clinical benefits. Consequently, the objective of this systematic review and meta-analysis was to evaluate the efficacy of corticosteroids on facial nerve regeneration and functional recovery following neurorrhaphy in the presence of complete axonal disruption.

Method

Eligibility Criteria

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement served as a reference for this review, which is why it was conducted according to its recommendations. We searched for randomised controlled trials (RCTs) that investigated the effectiveness of corticosteroid treatment following microsuture repair in patients who had experienced a full damage of the extratemporal facial nerve. Microsurgery was utilised to perform a repair that involved either a direct end-to-end anastomosis or a nerve interposition graft. Studies conducted on human subjects or animal subjects were both acceptable. After facial nerve coaptation, administrations of corticosteroids were taken into consideration for this study regardless of the route, dosage, frequency, or duration of treatment. The comparisons that were made were as follows: (1) systemic corticosteroid versus no corticosteroid (control); (2) local corticosteroid versus no corticosteroid (control); and (3) systemic corticosteroid versus local corticosteroid. randomised controlled trials (RCTs) that were published in languages other than English were one of the criteria for exclusion.

Search Strategy

The databases of Ovid MEDLINE and Ovid EMBASE were searched using the following search terms: "Dexamethasone OR Methylprednisolone OR Prednisolone OR Corticosteroids OR Triamcinolone OR Steroids OR Hydrocortisone OR Glucocorticoids" AND "Neurorrhaphy OR Nerve anastomosis OR Nerve suture OR Suturing method OR Suturing technique OR End-to-end. The most recent search was carried out on July, 2023. The references of the studies that were included in the analysis were combed through to look for any unpublished or missing published trials.

Data Extraction

The selection of the RCTs was done in a manner that was completely independent by the author. The author conducted their own independent review of the titles and abstracts, evaluating them based on the qualifying criteria that had been established. Complete versions of the articles that were chosen for review were read. The data that were extracted comprised the type of study, the number of participants, the type of animal, its age, its gender, the intervention, primary outcomes, and secondary outcomes.

The primary outcomes were two components of nerve regeneration, which comprised (1) electrophysiology, which evaluated the latency and amplitude values of electroneurography, and (2) histology, which evaluated axon diameter and myelin thickness. Both of these elements of nerve regeneration were studied. Secondary outcomes included an evaluation of functional recovery based on eye blinking, as well as adverse events.

Risk of Bias Assesment

The Cochrane Handbook for Systematic Reviews of Interventions was utilised in order to perform an analysis on the potential for bias within the studies that were included. The evaluation focused on five different areas: the production of

random sequences, the concealment of allocations, the blinding of participants and personnel, incomplete outcome data, and selective reporting.[13] When it came to the included studies, a low risk of bias could be found because the methodologies for each domain were detailed in detail. The study was deemed to have a high risk of bias in that area whenever the procedures that were provided for each domain demonstrated a high potential for bias. When there was insufficient data to evaluate the risk, the randomised controlled trial was categorised as having an ambiguous risk of bias.

Results

Study Selection

There were a total of 237 studies that were located and retrieved, 235 of which were the result of electronic searches and two of which were the result of human searches. After reviewing the titles and abstracts of the articles, we decided not to include 225 of them since they had irrelevant references. After reviewing the entire texts of the studies, we decided not to include six of them. The final qualitative synthesis included a total of six investigations, ranging from 26 to 31, with only three of those studies being included in the subsequent meta-analysis. Table 1 provides an overview of the listed studies' defining characteristics. Figure 1 displays, in the form of a flow chart, the process of the study's retrieval and selection.

Study Subjects

There was not a single human study that satisfied the requirements to be included. There were six studies total, and three of them used rats as models, while the other three used New Zealand rabbits. There were a total of 248 animals, 156 of which were Wistar rats (106 Wistar rats, Albino Wistar rats, and 50 Wistar rats), and 92 of which were New Zealand rabbits. In the Wistar rat models, 124 of the animals were male,[14,15] whereas the sexes of 32 of the animals could not be determined.[16] The weight of the rats ranged from 200 to 350 g. In one of the experiments[16], the participants were between 12 and 14 weeks old; however, in the other two trials, the age was not specified. In the New Zealand rabbit models, sixty of the animals were female, and the sexe of the remaining thirty-two animals could not be determined. The weight of the rabbits ranged anywhere from 1,200 to 3,000 grammes. In several of the rabbit model experiments, age was not a topic of discussion.

Intervention

The temperature ranged from 21 to 25◦C, and the humidity ranged from 10 to 55 percent. They were subjected to a cycle of light and dark that lasted for 12 hours and were given a typical diet. Intraperitoneal administration of ketamine hydrochloride (30–50 mg/kg) and xylazine hydrochloride (5–10 mg/kg) was the method used to bring on general anaesthesia. In each of the investigations that were included, a full transection of the facial nerve was performed on only one side, while the other side served as a control. Following surgery, every animal displayed signs of facial paralysis. An instantaneous repair using tension-free, end-to-end microsuture coaptation was accomplished with Prolene 8-0 in one study[16], Nylon 8-0 in one study[15], Prolene 9-0 in three studies[17–19], and Nylon 10-0 in the remaining research. Prolene 8-0 was used in one study, Nylon 8-0 was used in one study, and Prolene 9-0 was used in all of the investigations.[14] In four of the investigations[15,17–19], an epineural repair approach was used. A perineural suture was used in just one of the trials.[14] Nevertheless, the method of repair was not discussed in one of the studies.[16]

Outcomes

Electrophysiologic results

The nerve conduction test, performed with a Neuro-MEP 2 channel digital device at 10%–20% supramaximal intensity, was used to evaluate the electrophysiologic outcomes. Both the amplitude (millivolts) and the latency (milliseconds) were measured and recorded.

There were a total of three research[15–17] that assessed the value of latency. However, one study[17] did not report either the standard deviation or the 95% confidence interval. One randomised controlled trial (RCT)[15] investigated latency after topical treatment, while two trials[15,16] reported latency following systemic corticosteroid delivery. In the systemic route, the latency was evaluated after four weeks, after twelve weeks, and then at the conclusion of the trial. At any point in time, there was no discernible difference in delay between the groups receiving corticosteroids and those receiving a placebo: 4 weeks, 12-weeks, and the end of the study showed no significant differences.[15,16]

Four research provide the amplitude value.[14–17] did the analysis on the amplitude results. One study did not report the standard deviations or the 95% confidence intervals.[17] Three separate studies[14–16] examined amplitude following the injection of systemic corticosteroids, and two investigations looked at the results.[1415] examined the amplitude after applying the topical treatment. In the systemic group, the amplitude was evaluated at the beginning of the trial, after 4 weeks, 8 weeks, and more than 12 weeks had passed.[15,16] At each given time point, there were no significant variations in amplitude between the groups receiving corticosteroids and those receiving a control. 4 weeks, 8 weeks, and > 12 weeks respectively.[14–16]

Histologic result

After removing the portion of the facial nerve that had been coapted, it was then fixed in glutaraldehyde at a concentration of 2.5% and osmium tetroxide at a concentration of 1% and analysed using a transmission electron microscope (TEM). Quantitative measurements were taken of the axon diameter as well as the myelin thickness. In one randomised controlled trial (RCT), the effects of corticosteroids—both systemic and topical—on axon diameter and myelin thickness were

evaluated. Axon diameter: At the conclusion of the trial, one of the RCTs measured the axon diameter. The systemic corticosteroid group and the control group did not significantly differ from one another in terms of the diameter of their axons. The result was more favourable for the control group when it was compared to the group that had been exposed to the topical treatment. At the conclusion of the research project, there was no discernible change in the diameter of the axons between the topical treatment group and the systemic treatment group.[15]

Myelin thickness was measured by one of the RCTs, and this was done at the conclusion of the trial. The control group came out on top when it was put up against the group that received systemic steroids. The results of the comparison between the application of topical steroids and the control group preferred the control group. The results showed that the topical route of administration of steroids was superior than the systemic route of administration of corticosteroids.[15]

Functional result

A scale that was standardised was used to grade the amount of eye blinking that occurred. The eye blinking finding was reported in a single study. The function of blinking the eyes is: At the conclusion of the investigation, eye blinking was evaluated in one of the RCTs. When the control group was compared to the systemic administration of steroids, the results favoured the control group. The results of the comparison between the application of topical steroids and the control group preferred the control group. When the group receiving topical corticosteroids was compared to the group receiving systemic corticosteroids, the results supported the topical approach.[14]

Risk of Bias

There was only one study[14] that had a low risk of bias in the randomization and allocation concealment processes. Five studies[14–18] (showed a low risk of bias in blinding participants and professionals, accounting for 83.33% of the total. Five randomised controlled trials (RCTs)[14,16–18] had incomplete outcome data, but they were deemed to have a low risk of bias. Finally, three of the RCTs (50%) exhibited a low risk of bias in selective reporting.[14–16]

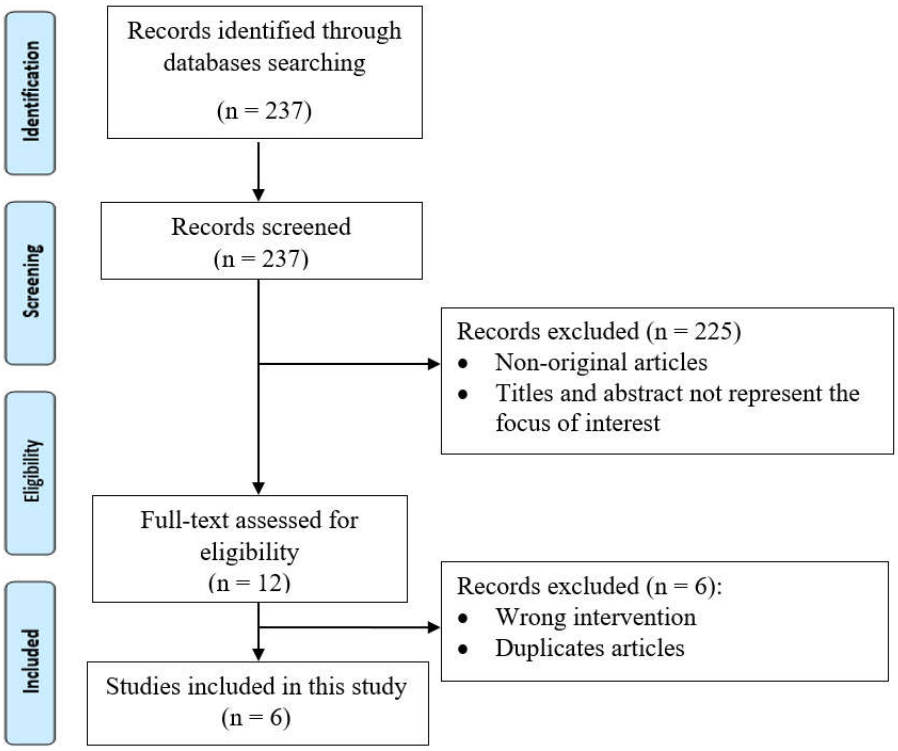

Figure 1. The search strategy based on PRISMA flow diagram

Table 1. Characteristics of the studis included

No	Author	Year	Animal	N	Site of FN	Type of intervention	Materials & methods	Time	Groups	Dose	Freq.	Dur.	Route	N per group
1	Karlidag et al.[18]	2011	New Zealand rabbit	30	Buccal branch	Complete transection with E t-E anastomosis	Prolene 9-0, epineural suture	8 wks.	Control	Received no medication				10
									N-Acetylcystein	50 mg/kg	OD	2 mo.	IM	10
									Methylprednisolone	1 mg/kg	OD	2 mo.	N/A	10
2	Seth et al.[14]	2012	Wistar rat	74	Left main trunk	Complete transection with tension-free microsuture coaptation	Nylon 10-0, perineural suture	8 wks.	Control (saline)	N/A	N/A	N/A	Local + IP	12

No	Author	Year	Animal	N	Site of FN	Type of intervention	Materials & methods	Time	Groups	Dose	Freq.	Dur.	Route	N per group
									Systemic dexamethasone-(+gelfoam saline)	1 mg/kg	12 h apart	3-times	IP	12
									Systemic dexamethasone-(+gelfoam saline)	5 mg/kg	12 h apart	3-times	IP	12
									Local dexamethasone-(+inject saline)	2 mg/mL	1-time Intraop	1-time	Local	12
									Local dexamethasone-(+inject saline)	4 mg/mL	1-time Intraop	1-time	Local	12
									Systemic dexamethasone-(+gelfoam saline)	0.5 mg/kg	12 h apart	3-times	IP	7
									Systemic dexamethasone-(+gelfoam saline)	10 mg/kg	12 h apart	3-times	IP	7
3	Yildirim et al.[19]	2014	New Zealand rabbit	30	Buccal branch	Nerve transection	Ethicon 9-0 epineural	8 wks.	Methylprednisolone	1 mg/kg	OD	3 wks.	IM	5
									Control	1 mL NSS	OD	3 wks.	IM	5
						Nerve compression	No repair		Methylprednisolone	1 mg/kg	OD	3 wks.	IM	5
									Control	1 mL NSS	OD	3 wks.	IM	5
						HSV type 1			Methylprednisolone	1 mg/kg	OD	3 wks.	IM	5
						inoculation			Control	1 mL NSS	OD	3 wks.	IM	5
4	Yanilmaz et al.[17]	2014	New Zealand rabbit	32	Left buccal branch	Complete transection with E-t-E anastomosis	Prolene 9-0 epineural repair	10 wks.	Control	No medication				8
									Aminoguanidine	100 mg/kg	OD	14d.	IP	8
									Melatonin	30 mg/kg	OD	10d.	IP	8
									Methylprednisolone	1 mg/kg	OD	15-18d.	IM	8
5	Edizer et al.[15]	2018	Albino Wistar rat	50	Left main trunk	Complete transection with E-t-E anastomosis	Nylon 8-0, epineural suture	13 wks.	Control (saline)	N/A	N/A	7d.	Local + IP	10
									Topical melatonin-(+IP saline)	Conc. 20 mg/mL	1-time	1-time	Local	10
									Systemic melatonin-(+ topical saline)	20 mg/kg	OD	7d.	IP	10
									Topical	Conc. 4 mg/mL	1-time	1-time	Local	10
									dexamethasone-(+ IP saline)					
									Systemic dexamethasone-(+ topical saline)	1 mg/kg	OD	7d.	IP	10
6.	Longur et al.[16]	2020	Wistar rat	32	Right main trunk	Full- thickness cut with E-t-E anastomosis	Prolene 8-0, mattress suture	28d.	Control	Received no intervention				8
									Bumetanide	15 mg/kg	OD	7d.	Gav.	8
									Dexamethasone	1 mg/kg	OD	7d.	IP	8
									Bumetanide + Dexamethasone	15 mg/kg +1 mg/kg	OD	7d.	Gav. + IP	8

Discussion

This systematic review revealed that neither systemic nor topical corticosteroids improved facial nerve regeneration in animal models following neurorrhaphy following complete transection. The regeneration of nerves was evaluated using electrophysiological, histologic, and functional measures. There were no statistically significant differences in latency or amplitude values between corticosteroids (both systemic and topical routes) and the control group, nor between systemic route and topical route. In terms of histologic and functional outcomes, neither systemic nor topical corticosteroids were superior to the control in terms of axon diameter, myelin thickness, and eye winking function.

According to a study by Yanilmaz et al.[17], the corticosteroid group exhibited greater axonal degeneration and myelin debris accumulation than the control group. Additionally, Schwann cell proliferation was diminished in the steroid group. Yildirim et al.[19] did not find any advantageous effects of methylprednisolone over a placebo on a histological outcome such as Schwann cell proliferation. In conclusion, these studies[17–19] demonstrated that corticosteroids had no effect on nerve regeneration following the complete disruption of the facial nerve, including nerve healing, Schwann cell proliferation, and myelin thickness.[18] In addition, corticosteroids may exacerbate facial nerve degeneration.[17,18]

Why corticosteroids help with partial nerve damage but not total axotomy remains a mystery. However, corticosteroids are thought to dampen the inflammatory response in the nervous system, protecting neurons from perioxidation and reducing neural and perineural inflammation.[5–7] Neurotmesis involves a more extensive and intricate neural injury and regeneration process than does a less severe form of nerve damage. Maybe that's why none of the promised benefits of corticosteroids were realised. More research is required to determine the precise cause.

In summary, there was insufficient evidence to support the routine use of corticosteroids in the treatment of complete facial nerve disruption followed by neurorrhaphy in humans. Although not specifically addressed in this review, high-dose corticosteroids have the potential to cause additional adverse effects, including but not limited to increases in blood glucose level, glaucoma or cataracts, and gastrointestinal irritation. As a result, the risks and advantages of using corticosteroids need to be carefully weighed before making any decisions.

This systematic review has limitations, including the fact that no human research were included in the analysis. In humans, clinical application still relies on the clinician's best discretion for each particular patient. Human randomised controlled trials (RCTs) should be supported going forward so that data can be trusted. However, in clinical practise, it may not be possible to conduct human studies with histology. This systematic review could only be used as guidance in clinical practise without human results. There was also a lack of quantity in this systematic review because of the little number of RCTs included in the analysis. This issue could be re-analyzed in the future if more RCTs are recruited and additional data is pooled.

Conclusion

This systematic review did not identify any potential benefits of systemic or topical corticosteroid administrations following facial nerve neurorrhaphy in cases of complete transection. In animal models, electrophysiologic, histologic, and functional recovery outcomes were used to evaluate the benefits. Possibly as a result of the limitations of histologic outcome measurement, all available recruited studies lacked human participants. This study should serve as a reminder to clinicians to consider the use of corticosteroids in such situations, and if practicable, prospective human clinical trials are suggested for future research.

References

[1]. Condie D, Tolkachjov SN. Facial Nerve Injury and Repair: A Practical Review for Cutaneous Surgery. Vol. 45, Dermatologic Surgery. 2019.
[2]. Lee PH, Liang CC, Huang SF, Liao HT. The outcome analysis of traumatic facial nerve palsy treated with systemic steroid therapy. J Craniofac Surg. 2018;29(7).
[3]. Pernambuco L, Espelt A, Góis ACB, de Lima KC. Voice Disorders in Older Adults Living in Nursing Homes: Prevalence and Associated Factors. J Voice [Internet]. 2017;31(4):510.e15-510.e21. Available from: http://dx.doi.org/10.1016/j.jvoice.2016.11.015
[4]. Aminoff MJ, Daroff RB. Encyclopedia of the Neurological Sciences. Encyclopedia of the Neurological Sciences. 2014.
[5]. Cayli SR, Kocak A, Yilmaz U, Tekiner A, Erbil M, Ozturk C, et al. Effect of combined treatment with melatonin and methylprednisolone on neurological recovery after experimental spinal cord injury. Eur Spine J. 2004;13(8).
[6]. Genovese T, Mazzon E, Crisafulli C, Di Paola R, Muià C, Bramanti P, et al. Immunomodulatory effects of etanercept in an experimental model of spinal cord injury. J Pharmacol Exp Ther. 2006;316(3).
[7]. Tsutsumi S, Ueta T, Shiba K, Yamamoto S, Takagishi K. Effects of the second national acute spinal cord injury study of high-dose methylprednisolone therapy on acute cervical spinal cord injury - Results in spinal injuries center. Spine (Phila Pa 1976). 2006;31(26).
[8]. Madhok VB, Gagyor I, Daly F, Somasundara D, Sullivan M, Gammie F, et al. Corticosteroids for Bell's palsy (idiopathic facial paralysis). Vol. 2016, Cochrane Database of Systematic Reviews. 2016.
[9]. Baugh RF, Basura GJ, Ishii LE, Schwartz SR, Drumheller CM, Burkholder R, et al. Clinical Practice Guideline: Bell's Palsy. Otolaryngol Neck Surg. 2013;149.
[10]. X. F, L. T, C. W, M. L, H. W, J. L, et al. A network meta-analysis to compare the efficacy of steroid and antiviral medications for facial paralysis from bell's palsy. Pain Physician. 2018;21(6).
[11]. Sun DQ, Andresen NS, Gantz BJ. Surgical Management of Acute Facial Palsy. Vol. 51, Otolaryngologic Clinics of North America. 2018.
[12]. Kannan RY, Hills A, Shelley MJ, Bisase B, Kapoor K, Norris P, et al. Immediate compared with late repair of extracranial branches of the facial nerve: a comparative study. Br J Oral Maxillofac Surg. 2020;58(2).
[13]. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343(7829).
[14]. Seth R, Revenaugh PC, Kaltenbach JA, Rajasekaran K, Meltzer NE, Ghosh D, et al. Facial nerve neurorrhaphy and the effects of glucocorticoids in a rat model. Otolaryngol - Head Neck Surg (United States). 2012;147(5).
[15]. Edizer DT, Dönmez Z, Gül M, Yiğit Ö, Yiğitcan B, Adatepe T, et al. Effects of melatonin and dexamethasone on facial nerve neurorrhaphy. J Int Adv Otol. 2019;15(1).
[16]. Longur ES, Yiğit Ö, Kalaycık Ertugay Ç, Araz Server E, Adatepe T, Akakın D, et al. Effect of Bumetanide on Facial Nerve Regeneration in Rat Model. Otolaryngol - Head Neck Surg (United States). 2021;164(1).
[17]. Yanilmaz M, Akduman D, Sagun ÖF, Haksever M, Yazicilar O, Orhan I, et al. The effects of aminoguanidine,

methylprednisolone, and melatonin on nerve recovery in peripheral facial nerve neurorrhaphy. J Craniofac Surg. 2015;26(3).
[18]. Karlidag T, Yildiz M, Yalcin S, Colakoglu N, Kaygusuz I, Sapmaz E. Evaluation of the effect of methylprednisolone and N-acetylcystein on anastomotic degeneration and regeneraton of the facial nerve. Auris Nasus Larynx. 2012;39(2).
[19]. Yildirim MA ki., Karlidag T, Akpolat N, Kaygusuz I, Keles E, Yalcin S, et al. The effect of methylprednisolone on facial nerve paralysis with different etiologies. J Craniofac Surg. 2015;26(3).