CORTICOSTEROIDS EFFECT ON ISOLATED OCULAR MOTOR NERVE PALSY DUE TO MICROVASCULAR ISCHEMIA : LONG-TERM FOLLOW-UP

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ABSTRACT

Introduction: Microvascular ischemia is the most common cause of isolated ocular motor nerve palsy in patients over 50 years old. Around 15-36% of those cases do not resolve and result in persistent diplopia. Until now, there is no proven management to speed up the resolution time and increase the resolution rate of those cases. This study aims to evaluate whether the resolution time and resolution rate of patients with isolated ischemia ocular motor nerve palsies who received corticosteroids were better than without corticosteroids.

Methods: This was an analytic observational study with a cross-sectional method. Data were collected retrospectively through patient's medical records at Cicendo National Eye Hospital from January to December 2019. Around 73 patients with isolated ischemia ocular motor nerve palsies were divided into 2 groups, which received corticosteroids and without corticosteroids.

Results: The median resolution time in the corticosteroids group was 4 weeks. This was faster than the non-corticosteroids group which was 12 weeks ($p = 0.007$). Around 82.9% of patients receiving corticosteroids had a complete resolution in the first 3 months whereas in the non-corticosteroids group only 47.4% of patients had complete resolution ($p = 0.001$). At 6 months follow-up, all patients in the corticosteroids group had resolution while 6 patients in the non-corticosteroids group had no resolution ($p = 0.279$).

Conclusion: Resolution time and resolution rates in the first 3 months in patients with isolated ischemia ocular motor nerve palsies who received corticosteroids were better than those without corticosteroids although the resolution rate at 6 months was not statistically significant.

Keywords: corticosteroids, ocular motor nerve palsy, isolated, microvascular ischemia

INTRODUCTION

Ocular motor nerve palsy is a neuro-ophthalmological case that is often encountered in daily clinical practice. It can occur in isolation (mononeuropathy) or in multiple concomitant paralyses of other cranial nerves (multineuropathy). Ogun et al. stated that 93.2% of cases of ocular motor nerve palsy occurred in isolation. The causes of this type of paralysis are generally acquired, and only a few are congenital. Chou et al. and Tamhankar et al. suggested that microvascular ischaemia is the most common cause of isolated ocular motor nerve palsy in patients over 50 years old.[1-6]

Isolated ocular motor nerve palsy due to microvascular ischemia generally resolves within 3-6 months with good control of risk factors. The study by Choi et al. showed that 64% of cases due to microvascular ischemia had complete resolution within three months and increased to

85% at six months. Other research by Dreyfus et al. showed that in cases of ocular motor nerve palsy due to diabetes mellitus, only nerve demyelination occurred without axon damage. It is believed that the majority of the recovery rates for ocular motor nerve palsy due to microvascular ischemia exhibit good results.[3,5,7,8]

Based on observations, it is highly likely that 15-36% of cases do not experience complete resolution. This will cause sequelae in the form of persistent diplopia, interfering with the patient's quality of life. Until now, no treatment can increase the resolution of ocular motor nerve palsy due to microvascular ischemia. The use of corticosteroids in ischemic cases is still a matter of debate. Corticosteroids can suppress inflammation which will trigger the neurodegeneration process and help reduce endoneurial edema. They also have the potential as neuroprotective agents that play a role in preventing the formation of connective tissue in nerve regeneration. To date, there have been no studies reporting the use of corticosteroids in isolated cases of ocular motor nerve palsy due to microvascular ischemia.[3,9-11] This study aimed to determine whether the timing and rate of resolution of patients with isolated motor ocular nerve palsy who received corticosteroids were better than those without corticosteroids.

METHOD

This study is an analytic observational study with a cross-sectional design. The study was conducted at the National Eye Center of Cicendo Eye Hospital (NEC-CEH) from May to September 2020. Sampling was carried out retrospectively through medical record data of patients who came to the Neuro-Ophthalmology Polyclinic NEC-CEH from January to December 2019. Data collection was carried out after obtaining approval from the Ethics Committee of the Faculty of Medicine, University of Padjadjaran, and NEC-CEH. The research subjects were patients with newly diagnosed isolated motor ocular nerve palsy due to microvascular ischemia and those aged over 50 years who met the inclusion criteria. The inclusion criteria in this study were patients who had never received corticosteroid therapy before, the onset of symptoms occurred within the first 30 days, had at least one risk factor for vasculopathy as evidenced by laboratory results, and were under treatment and supervision of an internal medicine specialist, followed up for up to 6 months and no other cause was found from the results of the neuroimaging examination.

Patients with congenital ocular motor nerve palsy, nuclear or supranuclear abnormalities, ocular myasthenia gravis, orbital disease, history of head trauma or previous malignancy, and were non-adherence to methylprednisolone, cyticoline, and methylcobalamin were excluded from the study. The research subjects were then divided into two groups: the corticosteroids group and the non-corticosteroids group. Corticosteroids group patients received oral methylprednisolone 1mg/kg BW/day in a single dose for one week (and tapered off subsequently), oral citicoline 1000

mg, and oral methylcobalamin 500 mg once a day. The group without corticosteroids were patients who received only a combination of oral cyticoline and methylcobalamin. The data taken were gender, age, onset of disease, vasculopathy risk factors and their number, ocular motor nerves involved, the severity of ocular motor nerve palsy, results of neuroimaging examination, treatment given, resolution time, and resolution rate.

The resolution rate consists of complete resolution, partial resolution, and no resolution. Resolution is considered complete if there is improvement in eye movement until its function returns to normal 100%. Partial resolution is obtained if there is improvement in eye movement, but its function has not returned to normal 100%. No resolution means that there is no improvement in eye movement at all. The data normality test was carried out before the significance test using the Shapiro Wilk test. The significance of numerical data was tested using the Mann-Whitney test, while the categorical data using the Chi-Square test, Fisher's Exact test, and Kolmogorov Smirnov test. The results are statistically significant if the p-value <0.05. Statistical analysis was performed using SPSS version 24.0 for Windows.

RESULT

A total of 73 patients' medical records meeting the inclusion and exclusion criteria were included in this study. Of those patients, 35 people were included in the group receiving corticosteroids, while 38 people were included in the non-corticosteroids group. A comparison of clinical characteristics in the two groups can be seen in table 1. In the corticosteroids group, most patients were male with a median age of 53 years, while in the group without corticosteroids, the majority of patients were female with a median age of 56 years. The abducens nerve is the most commonly involved ocular motor nerve, followed by the oculomotor and trochlear nerves. 42.9% of patients in the corticosteroids group and 42.1% of patients in the non-corticosteroids group presented with very mild ocular motor nerve palsy severity. The majority of patients in both groups had at least two risk factors for vasculopathy. Dyslipidemia is the most common risk factor for vasculopathy, followed by hypertension. Neuroimaging was only performed in 33 patients. The most commonly performed neuroimaging examination is a CT scan of the orbital head with contrast followed by MRI and MRA. From the analysis test, it can be concluded that the two groups are homogeneous (p>0.05).

Table 2 shows that the median value of resolution time in the corticosteroids group was four weeks; it was faster than the group without corticosteroids, which was 12 weeks (p=0.007; p<0.05). Table 3 shows that 82.9% of patients in the corticosteroids group experienced complete resolution in the first three months, while in the group without corticosteroids, only 47.4%. The chi-square test results showed a statistically significant difference between the two groups (p=0.001; p<0.05). At 6-month follow-up,

Table 1 Comparison of Clinical Characteristics in the Corticosteroids and Non-Corticosteroids Groups.

Variable	Groups		P values*
	Corticosteroids N=35	Non-Corticosteroids N=38	
Sex			**0.084**
Male	19 (54.3%)	13 (34.2%)	
Female	16 (45.7%)	25 (65.8%)	
Age (years)			**0.349††**
Median	53.00	56.00	
Range (min-max)	50.00-76.00	50.00-79.00	
Onset (weeks)			**0.085††**
Median	1.00	2.25	
Range (min-max)	1.00-4.00	1.00-4.00	
Vasculopathy Risk Factors			
Hypertension	21 (60.0%)	22 (57.9%)	**0.855**
Diabetes Mellitus	7 (20.0%)	13 (34.2%)	**0.174**
Dyslipidemia	29 (82.9%)	29 (76.3%)	**0.490**
Stroke	1 (2.9%)	2 (5.3%)	**1.000†**
Coronary Artery Disease	1 (2.9%)	0 (0.0%)	**0.479†**
Smoker	8 (22.9%)	5 (13.2%)	**0.279**
Number of Risk Factors			**0.792**
1 risk factor	8 (22.9%)	11 (28.9%)	
2 risk factors	22 (62.9%)	21 (55.3%)	
3 risk factors	5 (14.3%)	6 (15.8%)	
Ocular Motor Nerve Involvement			**0.989†††**
Oculomotor nerve palsy without puppilary involvement			
Complete	2 (5.7%)	3 (7.9%)	
Incomplete	10 (28.6%)	14 (36.8%)	
Trochlear nerve	7 (20.0%)	6 (15.8%)	
Abducens nerve	16 (45.7%)	15 (39.5%)	
Severity of Ocular Motor Nerve Palsy			**0.998**
Very mild	15 (42.9%)	16 (42.1%)	
Mild	7 (20.0%)	8 (21.1%)	
Moderate	5 (14.3%)	5 (13.2%)	
Severe	8 (22.9%)	9 (23.7%)	
Neuroimaging examination (n=33)			
MRI	5 (55.6%)	13 (54.2%)	**1.000†**
CT Scan	7 (77.8%)	15 (62.5%)	**0.407**
MRA	0 (0.0%)	1 (4.2%)	**1.000†**
CTA	0 (0.0%)	0 (0.0%)	**1.000**

†: Fisher's Exact test ††: Mann-Whitney U test †††: Kolmogorov Smirnov test *: significant if $p<0.05$.
MRI: Magnetic Resonance Imaging,CT scan: Computerized Tomography scan, MRA: Magnetic Resonance Angiography,CTA: Computerized Tomography Angiography

an increase in the number of patients with complete resolution in both groups was observed: 94.3% in the corticosteroids group and 71.1% in the non-corticosteroids group. Six patients or 15.8% of the group without corticosteroids had no resolution at all at the end of follow-up. However, based on the Kolmogorov Smirnov test, the difference between these two groups was not statistically significant ($p=0.279$; $p>0.05$).

Table 2 Comparison of Resolution Time in the Corticosteroids Group and Non-Corticosteroids Group

Variable	Groups		P values*
	Corticosteroids N=33	Non-Corticosteroids N=27	
Resolution time (weeks)			**0.007**†
Median	4.00	12.00	
Range (min-max)	1.00-24.00	2.00-24.00	

†: Mann-Whitney U test *: significant if p<0.05.

Table 4 shows that 13 patients, consisting of 2 patients from the corticosteroids group and 11 patients from the non-corticosteroids group, did not experience complete resolution at the last month's follow-up. Furthermore, seven patients experienced partial resolution, while the remaining six patients had no resolution. As many as 62% of patients had at least two vasculopathy risk factors, with the most vasculopathy risk factors being dyslipidemia with hypertension. CT scan and MRI results showed that multiple lacunar infarcts were found in 5 patients, cerebral infarct in 3 patients, cerebellar infarct in 1 patient, and the remaining four patients had no abnormalities.

Table 3 Comparison of Resolution Rates in the Corticosteroids Group and Non-Corticosteroids Group

Variable	Groups		P Values*
	Corticosteroids N=35	Non-Corticosteroids N=38	
Resolution Rate at 3 months			**0.001**†
Complete	29 (82.9%)	18 (47.4%)	
Partial	6 (17.1%)	10 (26.3%)	
None	0 (0.0%)	10 (26.3%)	
Resolution Rate at 6 months			**0.279**††
Complete	33 (94.3%)	27 (71.1%)	
Partial	2 (5.7%)	5 (13.1%)	
None	0 (0.0%)	6 (15.8%)	

†: Chi-Square test ††: Kolmogorov Smirnov test *: significant if p<0.05.

DISCUSSION

Microvascular ischemia is the most common cause of isolated ocular motor nerve palsy in patients over 50 years old with vasculopathy risk factors. The most common risk factors for vasculopathy in this study were dyslipidemia and hypertension. This is slightly different from that shown in the study of Jung et al. in the Korean population, where hypertension and diabetes mellitus were the two most common risk factors in patients with isolated ocular motor nerve palsy due to microvascular ischemia.[1,4,8,12]

The use of corticosteroids in ocular motor nerve palsy cases due to microvascular ischemia has not been reported; thus, there is no comparative study of the results of this study. Li et al. have reported that methylprednisolone can improve nerve function in experimental rats with sciatic nerve injuries. Methylprednisolone will increase the

thickness of the myelin sheath and inhibit the formation of connective tissue in nerve regeneration. Morisaki et al. also reported that glucocorticoids use could increase the expression of glucocorticoids receptors on Schwann cells which will trigger the remyelination process in experimental animal models of peripheral nerve trauma. In this study, the administration of corticosteroids was not aimed at repairing or restoring the ischemic process that occurred. It was to help repair and reduce the damages caused by the ischemic process so that they did not worsen. Therefore, it is essential to pay attention to good risk factor control to prevent a prolonged ischemic process.[9,11]

In this study, the corticosteroids used was oral methylprednisolone at a dose of 1 mg/kg BW. Morisaki et al. suggested that a corticosteroids dose of 1 mg/kg led to a more significant improvement in myelin by increasing myelin-binding protein levels than the group given a dose of 10 mg/kg. Excessive corticosteroids doses will have a negative effect by inhibiting the remyelination process in the peripheral nervous system. Methylprednisolone has drug interactions with the azole group and macrolide group, increasing the therapeutic effect of methylprednisolone. Antipsychotic drugs such as phenytoin and carbamazepine have been reported to decrease the therapeutic effect of methylprednisolone. Currently, there has been no reported drug interaction between methylprednisolone with cyticoline and methylcobalamin.[9,13,14]

Results showed that corticosteroids significantly increased the resolution rate to 82.9% in the first three months ($p=0.001$). These steroids also significantly increased the resolution time to 4 weeks from the usual 12 weeks ($p=0.007$). This acceleration in both resolution time and resolution rate was achieved through several mechanisms of action. Corticosteroids act as an anti-inflammatory both on vascular endothelium and on Schwann cells. They will stabilize the blood-nerve barrier by inhibiting the release of inflammatory mediators due to increased activity of the aldose reductase enzyme and will inhibit the release of phospholipase A2 in ischemic nerves. These steroids will also bind to ROS produced due to mitochondrial dysfunction in Schwann cells and increase NF-kB's release, which aggravates the neurodegeneration process.[9,10,15]

Experimental studies by Yang et al. in rats with spinal cord trauma showed that corticosteroids have a neuroprotective effect by increasing BDNF levels in glial cells. Another study by Sun et al. reported that dexamethasone had a synergistic effect with methylcobalamin in increasing BDNF expression in Schwann cells. BDNF is a neurotrophic factor that functions to prevent neuronal cell apoptosis, which leads to permanent damage. Corticosteroids also play a role in the neuroregeneration process by increasing the proliferation of Schwann cells through stimulation of the PMP22, MBP, and P0 proteins in Schwann cells and inhibiting fibroblast activity.

Table 4 Characteristics of Subjects Who Did Not Have a Complete Resolution at Sixth Month

No.	Groups	Sex	Age (years)	Onset (weeks)	Severity of Ocular Motor Nerve Palsy	Resolution Rate at 6 months	Vasculopathy Risk Factors	Number of Risk Factors	Ocular Motor Nerve Involvement	Neuroimaging results
1.	C	M	51	2	Moderate	Partial	HT, dyslipidemia	2	CN III complete	CT scan-MRI: multiple lacunar infarcts
2.	C	M	52	1	Very Mild	Partial	DM,dyslipidemia, smoker	3	CN IV	CT scan-MRI: multiple lacunar infarcts
3.	NC	M	61	4	Severe	Partial	HT, DM, dyslipidemia	3	CN III incomplete	CT scan: cerebral infarct
4.	NC	M	64	2	Moderate	Partial	Dyslipidemia	1	CN III complete	CT scan: normal
5.	NC	F	79	3	Severe	Partial	HT,dyslipidemia	2	CN VI	CT scan: normal
6.	NC	F	55	2.5	Mild	Partial	HT	1	CN VI	MRI: normal
7.	NC	F	55	2	Moderate	Partial	Dyslipidemia	1	CN VI	CT scan: cerebral infarct
8.	NC	M	63	2	Severe	None	Dyslipidemia, smoker	2	CN III incomplete	CT scan-MRI: multiple lacunar infarcts
9.	NC	F	60	3	Moderate	None	HT,dyslipidemia	2	CN III incomplete	MRI: multiple lacunar infarcts
10.	NC	F	70	3	Severe	None	HT,dyslipidemia	2	CN III incomplete	CT scan: cerebral infarct
11.	NC	F	60	2	Very Mild	None	HT	1	CN VI	MRI: multiple lacunar infarcts
12.	NC	M	63	4	Very Mild	None	HT,dyslipidemia	2	CN VI	CT scan: cerebellar infarct
13.	NC	F	51	1	Mild	None	HT	1	CN VI	CT scan: normal

C : Corticosteroids
NC : Non-Corticosteroids
HT : Hypertension
DM : Diabetes Mellitus

As a result, the axon regeneration process will not be hampered by excessive connective tissue formation.[16-18]

After six months, resolution rates between corticosteroids and non-corticosteroids groups were not statistically significant ($p = 0.279$). However, it was clear that all patients in the corticosteroids-treated group experienced resolution, while in the non-corticosteroids group, six patients (15.8%) showed no resolution. Both groups were given additional neuroprotector agents in the form of a combination of cyticoline and methylcobalamin. Methylcobalamin plays a role in the synthesis of phospholipids and myelin in the nervous system and can bind free radicals and increase brain-derived neurotrophic factor (BDNF) production, which plays a role in the nerve regeneration process.[10,19,20]

Cyticoline can reduce the production of phospholipase A2 and increase glutathione synthesis to prevent cellular oxidative stress. It also plays a role in the formation of phosphatidylcholine, which is important in forming cell membranes, increases acetylcholine's synthesis, and increases phospholipids' synthesis, including phosphatidylethanolamine, phosphatidylserine, which can repair axons and synapses. Administration of a combination of cyticoline and methylcobalamin alone does not seem to improve the time and rate of nerve resolution. Therefore, corticosteroids administration can be considered a treatment option in motor ocular nerve palsy cases due to microvascular ischemia. With faster resolution time and higher resolution, it is hoped that patients receiving corticosteroids will have a better quality of life.[10,21,22]

Table 4 shows that 13 patients did not have a complete resolution at the sixth month and 9 of them had abnormal neuroimaging results. The most common intracranial abnormality found in this study was multiple lacunar infarcts. This disorder has no causal relationship with ocular motor nerve palsy. It is similar to that found by Jung et al., where patients with isolated ischemic ocular motor nerve palsy who had intracranial abnormalities such as multiple lacunar infarcts on neuroimaging required a longer recovery time.[12]

As can be seen from table 4, other factors leading to 13 patients from both groups not experiencing complete resolution were age, onset, and the number of risk factors for vasculopathy. Most of those 13 patients were over 60 years old; obviously, the ability to regenerate the nervous system decreased with age. The study by Jung et al. also stated that more risk factors for vasculopathy would slow the resolution time of ischemic ocular motor nerve palsy. Further research is needed to ascertain the influence of these factors on the success rate of corticosteroids administration. The limitations of this study were that no study was conducted on a single corticosteroids group, or corticosteroids with citicoline alone, or corticosteroids with methylcobalamin alone. Moreover, the assessment of eye movement carried out by more than one ophthalmologist and the inability to match the research samples are also limitations in this study. This is due to the limited number of samples and retrospective data collection.[12,23]

CONCLUSION

Resolution time in patients with isolated ocular motor nerve palsy due to microvascular ischemia who received corticosteroids was faster than those without corticosteroids. In the first three months, the resolution rate in patients receiving corticosteroids treatment was better than those without corticosteroids; however, no significant difference was found between the resolution rates in the two groups after six months. Further study is needed to determine factors influencing the success rate of corticosteroids administration in isolated ocular motor nerve palsy cases due to microvascular ischemia and to discover the presence or absence of drug interactions between corticosteroids and other neuroprotective agents.

REFERENCES

1. Ogun OA, Olalekan O. Aremu OO, Ajaiyeoba AI. Ocular Motor Cranial Nerve Palsy as an Indicator of Neglected Systemic Disease in Nigeria: Perspective from a Neuro-Ophthalmology Clinic. Neuroophthalmology. 2019; 43(6): 355-62.
2. Fang C, Leavitt JA, Hodge DO, Holmes JM, Mohney BG, Chen JJ. Incidence and Etiologies of Acquired Third Nerve Palsy Using a Population-Based Method. JAMA Ophthalmol. 2017; 135(1): 23-8.
3. Choi KD, Choi SY, Kim JS, Choi JH, Yang TH, Oh SY, et al. Acquired Ocular Motor Nerve Palsy in Neurology Clinics: A Prospective Multicenter Study. J Clin Neurol. 2019; 15(2): 221-7.
4. Kung NH, Van Stavern GP. Isolated ocular motor nerve palsies. Semin Neurol. 2015; 35: 539-48.
5. Tamhankar MA, Biousse V, Ying GS, Prasad S, Subramanian PS, Lee MS, et al. Isolated third, fourth, and sixth cranial nerve palsies from presumed microvascular versus other causes: a prospective study. Ophthalmology. 2013; 120: 2264-9.
6. Chou KL, Galetta SL, Liu GT, Volpe NJ, Bennett JL, Asbury AK, et al. Acute ocular motor mononeuropathies: prospective study of the roles of neuroimaging and clinical assessment. J Neurol Sci. 2004; 219: 35-9.
7. Richner M, Ferreira N, Dudele A, Jensen TS, Vaegter CB, Gonçalves NP. Functional and Structural Changes of the Blood-Nerve-Barrier in Diabetic Neuropathy. Front Neurosci. 2019; 12(1038): 1-9.
8. Galtrey CM, Schon F, Nitkunan A. Microvascular Non-Arteritic Ocular Motor Nerve Palsies—What We Know and How Should We Treat? Neuro-Ophthalmology. 2015; 39(1): 1–11.
9. Morisaki S, Nishi M, Fujiwara H, Oda R, Kawata M, dan Kubo T. Endogenous Glucocorticoids Improve Mielination via Schwann Cells After Peripheral Nerve Injury: An In Vivo Study Using a Crush Injury Model. Glia. 2010; 58: 954–63.
10. Mekaj A dan Mekaj Y. The Role of Pharmacological Agents in Nerve Regeneration after Peripheral Nerve Repair. Dalam: Mauricio AC, editor. Peripheral Nerve Regeneration: From Surgery to New Therapeutic Approaches Including Biomaterials and Cell-Based Therapies Development. London: IntechOpen; 2017. hlm. 147-74.

11. Li Q, Li T, Cao XC, Luo DQ, Lian KJ. Methylprednisolone microsphere sustained-release membrane inhibits scar formation at the site of peripheral nerve lesion. Neural Regeneration Research. 2016; 11: 835-41.
12. Jung JS, Kim DH. Risk Factors and Prognosis of Isolated Ischemic Third, Fourth, or Sixth Cranial Nerve Palsies in the Korean Population. J Neuro-Ophthalmol. 2015; 35: 37-40.
13. Bailie GR, Jhonson CA, Mason NA. Med facts: Pocket guide of drug interaction. Edisi ke-2. Nephrology Pharmacy Associates. 2004: 40-1.
14. Brophy KM, Scarlett-Ferguson H, Webber KS, Abraham AC, Lammon SB. Clinical drug therapy for Canadian practice. Chapter 23 Corticosteroids. Lippincott Williams and Wilkins. 2010: 370-1.
15. Madalena KM, Lerch JK. The effect of glucocorticoid and glucocorticoid receptor interactions on brain, spinal cord, and glial cell plasticity. Neural Plast. 2017; 11(1): 37-41.
16. Yang J, Xu ZG, Rong R, Lü ZP, Sun YH, Zhao Y, et al. Effect of methylprednisolone on neurological behavior and the BDNF and NMDA receptor expression after traumatic spinal cord injury in rats. Sichuan da xue xue bao. 2012; 43(2):245-9.
17. Sun H, Yang T, Li Q, Zhu Z, Wang L, Bai G, et al. Dexamethasone and vitamin B(12) synergistically promote peripheral nerve regeneration in rats by upregulating the expression of brain-derived neurotrophic factor. Arch Med Sci. 2012; 9: 8(5): 924-30.
18. Desarnaud F, Bidichandani S, Patel PI, Baulieu EE, Schumacher M. Glucocorticosteroids stimulate the activity of the promoters of peripheral myelin protein-22 and protein zero genes in Schwann cells. Brain Research. 2000; 865(1):12-6.
19. Tezcan AH. Peripheral Nerve Injury and Current Treatment Strategies. Dalam: Mauricio AC, editor. Peripheral Nerve Regeneration: From Surgery to New Therapeutic Approaches Including Biomaterials and Cell-Based Therapies Development. London: IntechOpen; 2017. hlm. 3-31.
20. Nishimoto S, Tanaka H, Okamoto M, Okada K, Murase T, Yoshikawa H. Methylcobalamin promotes the differentiation of Schwann cells and remielination in lysophosphatidylcholine-induced demielination of the rat sciatic nerve. Front Cell Neurosci. 2015; 9(298): 1-13.
21. Jasielski P, Piedel F, Piwek M, Rocka A, Petit V, Rejdak K. Application of Citicoline in Neurological Disorders: A Systematic Review. Nutrients. 2020; 12(10): 3113.
22. Ozay R, Bekar A, Kocaeli H, Karl N, Filiz G, Ulus IH. Citicoline Improves Functional Recovery, Promotes Nerve Regeneration, and Reduces Postoperative Scarring After Peripheral Nerve Surgery in Rats. Surgical Neurology. 2007; 68: 615-22.
23. Mizisin AP, Weerasuriya A. Homeostatic regulation of the endoneurial microenvironment during development, aging and in response to trauma, disease and

toxic insult. Acta Neuropathol. 2011; 121: 291–312.