ISSN 2706-6819 Vol.4, Issue 10: 16-23, DOI: 10.25236/IJFM.2022.041004

New Research Advances in the Treatment of Nonarteritic Anterior Ischemic Optic Neuropathy

Shizhou Cheng[1,a], Chuyun Xing[2,b], Zuhai Zhang[1,c,*]

[1]The First Affiliated Hospital of Yangtze University, Jingzhou, China
[2]Jingzhou Hospital Affiliated to Yangtze University, Jingzhou, China
[a]shizhou_Cheng@163.com, [b]chuyun_Xing@163.com, [c]zuhai_zhang@outlook.com
**Corresponding author*

Abstract: *Ophthalmic diseases evidently affect people's daily lives. Nonarteritic anterior ischemic optic neuropathy (NAION) is an acute optic neuropathy and has a complex etiology and pathogenesis. NAION causes acute ischemia and structural and functional disorders of the optic nerve resulting from insufficient perfusion of the short posterior ciliary artery. NAION may cause irreversible vision loss, visual field defects, and even blindness if it is not treated early. There is no definite and standard treatment plan for NAION. To treat NAION more effectively, herein, we reviewed the clinical treatment of NAION in recent years and the latest treatment research progress, which will provide a systematic guidance for the treatment of NAION.*

Keywords: *Nonarteritic anterior ischemic optic neuropathy, Ischemic optic neuropathy, Treatment*

1. Introduction

Optic nerve disease is a relatively common and difficult emergency in the ophthalmology field that leads to impaired vision. The optic nerve is mainly formed by the axonal fibers of the retinal ganglion cells (RGCs) that extend from the retina to the optic papilla in all directions. The RGCs of the optic nerve transmit visual signals to the visual center; therefore, apoptosis of the RGCs can result in a lesion of the optic nerve conduction pathway and thus cause a failure in neural excitation transmission to the brain to produce vision. Ischemic optic neuropathy (ION) is a common optic nerve disease that seriously endangers visual function. ION has many types, and nonarteritic anterior ischemic optic neuropathy (NAION) is the most common type, mostly with a monocular onset. Systemic factors, such as hypertension, nocturnal hypotension, diabetes mellitus, hyperlipidemia, atherosclerosis, and obstructive sleep apnea, and local factors, such as anisometropia, microphthalmia, abnormal relative position of the posterior short ciliary artery watershed and optic papilla, and extrusion of the optic disc, are important risk factors for the development of NAION[1-4]; however, its exact pathogenesis is not completely understood. NAION is mainly caused by insufficient blood supply to the posterior ciliary artery. It is common in middle-aged and older adults, with an incidence of 2.3–10.2/100,000 in the United States and 1/16,000 in China[5, 6]. Furthermore, Caucasians account for 95% of patients with NAION in the United States, implying that there are racial differences in the incidence of NAION[7]. This review provides a systematic guidance for the treatment of NAION through an analysis of the pros and cons of various treatment modalities in the past and latest advances to achieve early prevention and standardized treatment for controlling disease progression.

2. Treatment modality

At present, due to insufficient understanding of the pathogenesis of NAION, the overall treatment effect of NAION is still unsatisfactory, and there is no clinically definite, standard, and effective treatment method. The treatment is mainly causative, pharmacological, surgical, exocrine, combined medication, and Chinese medicine, whose main objectives are to protect RGCs, rapidly eliminate optic nerve edema, and effectively improve the visual function of patients.

ISSN 2706-6819 Vol.4, Issue 10: 16-23, DOI: 10.25236/IJFM.2022.041004

2.1 Etiological treatment

2.1.1 Systemic diseases

In recent years, certain risk factors associated with the development of NAION have been identified; furthermore, systemic underlying diseases, such as hypertension, hyperlipidemia, and hyperglycemia, which can cause atherosclerosis, are closely related to NAION and can increase the risk of its development. Therefore, early detection, diagnosis, and active treatment of the primary disease play a vital role in preventing the development of NAION.

2.1.2 Hyperbaric oxygen therapy and phosphodiesterase-5 inhibitor (PDE5I) drugs

Hypoxia causes abnormalities in the metabolism, morphological structure, and function of the ocular tissues; hyperbaric oxygen therapy can improve the hypoxic state of the ocular tissues by increasing the oxygen content in the blood, reducing the local inflammatory reaction of the eye, and protecting the optic nerve. Weimin Zhou et al. conducted a study on 110 patients with NAION and found that the total effective treatment rate was higher in patients treated with hyperbaric oxygen therapy (83.63%) than in the controls not treated with hyperbaric oxygen therapy (74.55%); thus, the comprehensive treatment of hyperbaric oxygen therapy could significantly improve the visual acuity and field, and reduce the inflammatory response in patients with NAION, which is beneficial for improving the clinical efficacy[8]. Appropriate supplementation with hyperbaric oxygen therapy is helpful in improving ocular ischemia in and visual quality of patients with NAION. At the same time, ingestion of PDE5I drugs, such as sildenafil, can cause relaxation and vasodilation of the vascular smooth muscle, reduce blood flow to the optic nerve head through systemic hypotension, and also increase the risk of NAION[9]. Therefore, rational use of PDE5I drugs is important to reduce the risk of development of NAION.

2.1.3 Vascular regulation function

Obstructive sleep apnea syndrome is a long-term chronic intermittent hypoxia and carbon dioxide retention in the body's internal environment caused by impaired central respiratory regulation and upper airway obstruction, resulting in a series of pathophysiological changes, including oxidative stress, associated inflammation, vascular damage, and metabolic disorders[10-14]. It has important implications for further understanding the pathogenesis of NAION and further research on the treatment of NAION in terms of vascular regulatory function.

2.2 Medication treatment

The latest research reports that the use of steroid hormones can improve the visual function of patients but also further aggravate the disease[15]; it may also induce the development of NAION in the contralateral eye[16]. Therefore, the advantages and disadvantages of steroid hormone treatment for NAION, including the timing, control, dosage of steroids, and specific treatment methods, should be further discussed and studied. At present, the efficacy and safety of drugs for protecting the optic nerve cells are uncertain, such as vinblastine and its derivatives, estrogen analogs, and puerarin, which have protective effects on RGCs [17, 18] but also have corresponding side effects. The research prospect of such drugs is promising. Compound anisodine and other autonomic nerve modifiers can improve edema and ischemia in the optic nerve, promote recovery of the optic nerve, and thus improve visual function[19]; they have been widely used in the clinical treatment of AION. Mecobalamin is a form of vitamin B12 used for the treatment of optic nerve injury. The study on the treatment of AION with mecobalamin combined with various drugs showed that the overall recovery of visual function of patients in the combined drug group was better than that of those in the single drug group [20], indicating that mecobalamin tablets, as an auxiliary drug for the treatment of AION, can effectively improve the visual function of patients, which is worthy of clinical importance and application. At present, anticoagulants are also used for the treatment of NAION [21]; however, considering the risk of systemic and local bleeding, they are rarely used. Moreover, many experts recommend using aspirin after the initial bout of NAION [5]. Foroozan et al. conducted a retrospective cohort study on 431 patients with unilateral NAION and concluded that aspirin may have short-term benefits but it cannot provide long-term protection[22]. Therefore, the use of aspirin in the treatment of NAION needs further validation and research.

ISSN 2706-6819 Vol.4, Issue 10: 16-23, DOI: 10.25236/IJFM.2022.041004

2.3 Surgical treatment

2.3.1 Optic nerve decompression

Optic nerve decompression surgery (ONDS) focuses on creating two or more windows in the tissue surrounding the optic nerve to allow the cerebrospinal fluid to flow out. Theoretically, the use of ONDS can reduce nerve and vascular compression due to edema; however, related trials have demonstrated that the visual acuity improvement and prognosis of patients after ONDS is not satisfactory[23].

2.3.2 Transvitreous optic neurotomy

The purpose of transversal optic neurotomy is to open the scleral canal and relieve the pressure on the edematous optic papilla. Soheilian et al. have reported the outcomes of seven cases of acute NAION and severe visual loss with optic neurotomy and preoperative onset from 15 to 90 days. They observed improvement in the visual acuity of six patients. However, this study was limited by the small number of patients, delay in treatment initiation, sample bias, and lack of clinical guidance importance[24]. Thus, large clinical trials are needed to assess the efficacy of transversal optic neurotomy for NAION.

2.3.3 Intravitreal drug injection

*(1) Anti-vascular endothelial growth factor (VEGF) drugs***.** Anti-VEGF drugs reduce inflammatory response, decrease vascular permeability, and promote the regression of optic disc edema. Furthermore, an intravitreal injection of bevacizumab for NAION reduces optic disc edema and improves visual acuity in patients[25, 26]. However, the results of the study by Rootman et al. did not reveal any improvement in visual acuity or retinal peripheral nerve fiber layer thickness[27]. Therefore, the efficacy of vitreous cavity injections of anti-VEGF drugs for the treatment of patients with NAION is not conclusive, and further studies are needed to assess it.

*(2) Rho kinase inhibitor***.** Intravitreal injection of fasudil (IVF), a Rho kinase inhibitor and vasodilator, inhibits the release of inflammatory factors or blocks inflammatory factor action pathways [28] and also regulates the differentiation of nerve repair[29]. Sanjari et al. administered IVF in 13 patients with recent NAION episodes and saw that the patients showed significant improvement in visual acuity and significant changes in the peripapillary retinal nerve fiber layer[30]. IVF may be an effective treatment for NAION; however, the sample size of such studies is currently small, and further extensive studies on its efficacy are required.

(3) Erythropoietin (EPO). EPO and its receptors are expressed in the central nervous system and involved in neuroprotection and regeneration[31]. Modarres et al. administered a vitreous cavity injection of EPO in 31 patients with NAION and observed that 27 (87%) eyes had improved visual acuity 6 months after treatment[32]. However, there is a lack of sufficient evidence from clinical studies on the therapeutic effects of NAION.

(4) Prostaglandin J2 (PGJ2). PGJ2 is a prostaglandin derivative with anti-inflammatory and neuroprotective properties[33]. Miller et al. evaluated the effects of vitreous cavity injection of PGJ2 in an animal model of NAION and found that PGJ2 promoted the regression of optic disc and peripapillary edema, reduced nerve fiber layer thickness, and protected surviving nerve axons; no systemic or ocular toxicity or other adverse effects were found, providing a theoretical basis for future clinical research applications[34].

(5) Granulocyte colony-stimulating factor. Study Shows Neuroprotective Effects of Subcutaneous Granulocyte Colony Stimulating Factor (G-CSF) Injection in a Rat Model of NAION[35]. Abri et al. administered an intravitreal injection of G-CSF to 14 (14 eyes) patients with NAION. The best corrected visual acuity significantly improved in the first month after treatment, then decreased, and finally, (12 months later) did not improve significantly. A significant reduction in the retinal nerve fiber layer thickness was observed in all quadrants compared with the baseline measurements. At the same time, no improvement in visual field parameters was observed, and no significant changes in toxicity were recorded[36]. It is presumed that a vitreous cavity injection of G-CSF is safe; however, the exact dose of injection and duration of treatment are unclear and need to be further evaluated in numerous clinical studies.

(6) Small interfering ribonucleic acid (siRNA). A new development has emerged in recent years at the frontier of optic nerve protection research, where it has been shown that siRNA can prevent apoptosis by inhibiting the Caspase-2 expression[22]; intravitreal injection of siRNA is at the forefront of neuroprotection research[2]. RGC loss after optic nerve injury is one of the hallmarks of AION, and

ISSN 2706-6819 Vol.4, Issue 10: 16-23, DOI: 10.25236/IJFM.2022.041004

studies have demonstrated that 80% of RGCs are cleared within 14 days in an optic nerve severed rat model, and caspase-2 is expressed and predominantly cleaved (activated) in RGCs. The inhibition of caspase-2 expression by an intravitreal injection of chemically modified synthetic siRNA significantly improves RGC survival for at least 30 days[37]. Optic nerve injury-induced RGC apoptosis involves caspase-2 activation, and synthetic siRNAs designed to inhibit caspase-2 expression represent potential neuroprotective agents for intervention in human diseases involving RGC loss. Solano et al. have reported the toxicological and pharmacokinetic properties of the synthetic small interfering RNA (siRNA) QPI-1007, a chemically modified siRNA designed to temporarily inhibit caspase 2 protein expression via the RNA interference pathway and developed as a neuroprotective agent for the treatment of NAION and other optic neuropathies, after intravitreal administration, with results suggesting a low risk of systemic toxicity; QPI-1007 was negative in all three genotoxicity studies[38]. Overall, non-clinical studies support further development of QPI-1007. Moreover, the mechanism of action, treatment dose, and treatment course of vitreous cavity injection of siRNA to protect the optic nerve in NAION treatment will be a hot topic for research, which of course requires the joint efforts of clinical and basic research to promote research progress and bring greater breakthroughs in NAION treatment.

2.4 Mesenchymal stem cell (MSC)-derived exosome therapy

The tissue repair and immunomodulatory effects of MSCs based on different cell sources have emerged as the most promising strategy for the treatment of ischemic diseases of various tissue origins[39-41]. MSC-exosomes contain cell-specific proteins and nucleic acids of MSC origin that can partially mimic the function of MSCs and can cross the blood–cerebrospinal fluid barrier, allowing them to replace MSCs in the recanalization therapy of ischemic diseases, thus becoming a potentially effective treatment option for NAION. The following are the main mechanisms of action of MSC-exosomes in the treatment of AION: 1) Intravenous MSCs rescue retinal laser damage by inhibiting the inflammatory response and reducing apoptosis, but they are less likely to migrate to the damaged retina. Yu et al. observed and compared their functions in a mice model of laser-induced retinal injury by an intravitreal injection of MSCs and their exosomes from a mouse adipose tissue or the human umbilical cord and found that both MSCs and their exosomes reduced cell damage and apoptosis and inhibited inflammatory responses[42]. Xiao et al. showed that exosomes derived from bone marrow mesenchymal stem cells (BMSCs) can inhibit the apoptosis of oligodendrocytes [43]. Yu and Li et al. have also suggested that MSC-exosomes inhibit inflammatory responses and reduce neuronal cell injury and apoptosis [44, 45]. 2) Human umbilical cord MSC-exosomes were found to reduce the intensity of ongoing experimental autoimmune uveoretinitis by reducing infiltration of intraocular T-cell subsets and other inflammatory cells, thereby protecting the retinal structure and rescuing retinal function[46]. MSC-exosomes are hypoimmunogenic and also activate immunomodulatory-related signaling pathways. 3) Mead et al. demonstrated significant neuroprotective and anxiogenic effects (promoting neuroplasticity) and the ability to maintain retinal function in BMSCs-derived exosomes, wherein exosomes successfully transported substances to the inner retinal layers and RGCs and produced therapeutic effects through miRNA-dependent mechanisms[47]. 4) Song et al. used optical coherence tomography angiography to evaluate 30 patients with NAION and 30 normal subjects and found that both superficial peripapillary and optic disc vascular density was significantly lower in the NAION group than in the control group, confirming that there is inadequate blood perfusion and loss of microvessels in the retina and optic disc in NAION and that vascular neovascularization is one of the key factors in the repair of post-ischemic damage[48]. Moisseiev et al. showed that an intravitreal injection of human MSC-exosomes from cultures cultured under hypoxic conditions significantly reduced retinal ischemia and promoted neovascularization in a mouse model of oxygen-induced retinopathy[49]. Weiss et al. treated 10 patients with NAION with bone marrow stem cells and found that visual acuity improved in 73.6% of eyes after treatment, suggesting that the possible mechanisms for visual improvement include paracrine secretion of proteins and hormones from the bone marrow stem cells, mitochondrial transfer, the release of messenger RNA or other compounds via exosomes or microvesicles, and neuronal transdifferentiation of stem cells[50]. Therefore, MSC-exosomes have a broad research prospect for the clinical treatment of NAION, including injection methods (vitreous cavity injection, intravenous injection, and retrobulbar injection), treatment dose, and treatment time, which will be a hot research topic. However, Li et al. indicated that the use of BMSCs has certain disadvantages, such as potential tumorigenicity, the need for autologous collection, and short survival time [45], suggesting that some of the same problems and other potential risks not yet identified exist after the application of MSC-exosomes for clinical treatment, which needs to be further verified and clarified.

ISSN 2706-6819 Vol.4, Issue 10: 16-23, DOI: 10.25236/IJFM.2022.041004

2.5 Combination drug therapy

Many studies have shown that the combination of multiple drugs can have a corresponding synergistic effect and enhance drug efficacy, and a combination of drugs is often used clinically to treat NAION. Liu Aqin observed 88 (88 eyes)patients with NAION in the early stages and found that the total effective rate of the observation group was 84.09%, which was higher than that of the control group; they also found that the improvement of blood rheology index level by the combination of Gekisin injection with conventional western medicine was better than that of conventional western medicine treatment alone [51]. G-CSF combined with meloxicam reduces the infiltration and destruction of the optic nerve by leukocytes and macrophages, providing a synergistic effect on neuroprotection[52]. The overall therapeutic effect of the combination of multiple drugs in the treatment of NAION is considerable and effectively improves the visual function of patients; however, the standard of rational compounding should be followed in the process of clinical combination of drugs to achieve maximum efficacy in the treatment of NAION.

2.6 Traditional Chinese Medicine Treatment

AION belongs to the category of “dimness of vision” and “violent blindness” in Chinese medicine, which is most common in middle-aged and elderly people. It has been found that Chinese medicine treatment (Chinese medicine preparation and acupuncture treatment) has specific efficacy in improving blood rheology and microcirculation [53-55], and has shown significant clinical effects. Yufang Su conducted a study on 50 patients with NAION; 25 patients in the treatment groups were provided TCM acupuncture therapy and 25 patients in the control group were administered compound camptothecin injection. It was found that acupuncture therapy was superior to superficial temporal artery injection of compound camptothecin, which effectively promoted visual repair and improved the visual field in NAION [56]. In a study, Zhao Di collected 82 (96 eyes) patients with AION; 41 (48 eyes) patients in the control group were treated with Ginkgo biloba extract injection, and 41 (48 eyes) patients in the observation group were treated with Blood Activating and Tongluo Formula plus and minus. It was found that the treatment efficacy rate of the observation group was 70.08%. The results showed that the efficacy of the treatment of AION with the addition and subtraction of the blood circulation formula was significant[57]. Traditional Chinese medicine has effectively improved visual function. Although acupuncture treatment has a significant effect, the location of acupoints and the methods of acupuncture need to be further studied.

3. Conclusion

In this review, we have provided an important summary on the treatment of NAION, including the advantages and disadvantages of previous conventional treatments and the latest research advances in treatment, thus further improving the understanding of NAION and providing new ideas for further clinical treatment and basic research of NAION.

Etiological treatment can prevent NAION to some extent. Although early steroid hormone treatment has certain efficacy, it has more side effects and even aggravates disease progression. Although conventional Western medicine treatments have some effects on NAION, significant effective treatment has not been seen. The effect is more obvious with the combination of multidrug treatment. Surgical treatment is currently less used in clinical practice, and a vitreous cavity injection of relevant drugs is the main treatment modality for NAION. The vitreous cavity injection of siRNA is a new development in optic nerve protection research, but it is currently limited to the animal research stage. Moreover, clinical trials are still at the stage of recruiting patients; however, its low toxicity risk and significant efficacy from animal trials also provide a new direction for the treatment of NAION. MSC-exosomes have the advantages of targeting small molecules, and significant efficacy but may have the disadvantages of potential tumorigenicity and short survival time. There is still a lack of comprehensive understanding of MSC-exosomes, whether in clinical applications or basic research, and they will remain an important topic for research in the future. From the current clinical treatments, TCM is more effective (no adverse effects have been reported) and has great clinical value. The current treatment protocol for NAION has shifted from monotherapy to a combination of multiple therapies, achieving better results.

NAION has a complex etiology; thus, its exact pathogenesis has not been confirmed, indicating that there is no uniform and clear treatment plan for NAION. Therefore, the treatment effect on NAION is

ISSN 2706-6819 Vol.4, Issue 10: 16-23, DOI: 10.25236/IJFM.2022.041004

still unsatisfactory. The pathogenesis of NAION needs to be studied in more depth to provide further guidance for the treatment of NAION. Moreover, for the existing treatment modalities, some disadvantages should be further improved, such as the complications involved in ONDS surgery and the non-ideal postoperative and long-term prognosis. For steroid hormone treatment, it should be further clarified whether it aggravates the disease or induces the development of NAION in the contralateral eye and whether discontinuation of steroid hormones should be considered in future treatment. We believe that more effective treatment options will emerge by further exploration of NAION.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

[1] M. H. Sun, C. Y. Lee, Y. J. Liao, and C. C. Sun, Nonarteritic anterior ischaemic optic neuropathy and its association with obstructive sleep apnoea: a health insurance database study. Acta Ophthalmol, 2019. 97(1): p. e64-e70.
[2] S. Berry, W. V. Lin, A. Sadaka, and A. G. Lee, Nonarteritic anterior ischemic optic neuropathy: cause, effect, and management. Eye Brain, 2017. 9: p. 23-28.
[3] Y. Wu, L. M. Zhou, H. Lou, J. W. Cheng, and R. L. Wei, The Association Between Obstructive Sleep Apnea and Nonarteritic Anterior Ischemic Optic Neuropathy: A Systematic Review and Meta-Analysis. Curr Eye Res, 2016. 41(7): p. 987-92.
[4] S. Moghimi et al., Crowded optic nerve head evaluation with optical coherence tomography in anterior ischemic optic neuropathy. Eye (Lond), 2017. 31(8): p. 1191-1198.
[5] N. R. Miller and A. C. Arnold, Current concepts in the diagnosis, pathogenesis and management of nonarteritic anterior ischaemic optic neuropathy. Eye (Lond), 2015. 29(1): p. 65-79.
[6] L. Xu, Y. Wang, and J. B. Jonas, Incidence of nonarteritic anterior ischemic optic neuropathy in adult Chinese: the Beijing Eye Study. Eur J Ophthalmol, 2007. 17(3): p. 459-60.
[7] M. A. Warner, Cracking open the door on perioperative visual loss. Anesthesiology, 2012. 116(1): p. 1-2.
[8] W. Zhou et al., Clinical effect of hyperbaric oxygen combined therapy on patients with non-arteritic anterior ischemic optic neuropathy. Chinese Journal of Nautical Medicine and Hyperbaric Medicine, 2021. 28(1): p. 5 (in Chinese).
[9] A. G. Distefano and B. L. Lam, Non-Arteritic Anterior Ischemic Optic Neuropathy in Pilots. Aerosp Med Hum Perform, 2018. 89(11): p. 1005-1007.
[10] L. Lavie, Oxidative stress in obstructive sleep apnea and intermittent hypoxia--revisited--the bad ugly and good: implications to the heart and brain. Sleep Med Rev, 2015. 20: p. 27-45.
[11] A. Maniaci et al., Oxidative Stress and Inflammation Biomarker Expression in Obstructive Sleep Apnea Patients. J Clin Med, 2021. 10(2).
[12] A. Gabryelska, Z. M. Lukasik, J. S. Makowska, and P. Bialasiewicz, Obstructive Sleep Apnea: From Intermittent Hypoxia to Cardiovascular Complications via Blood Platelets. Front Neurol, 2018. 9: p. 635.
[13] F. F. de Lima, D. R. Mazzotti, S. Tufik, and L. Bittencourt, The role inflammatory response genes in obstructive sleep apnea syndrome: a review. Sleep Breath, 2016. 20(1): p. 331-8.
[14] J. W. Ycas, Toward a Blood-Borne Biomarker of Chronic Hypoxemia: Red Cell Distribution Width and Respiratory Disease. Adv Clin Chem, 2017. 82: p. 105-197.
[15] J. Chen, J. Zhu, L. Chen, C. Hu, and Y. Du, Steroids in the treatment of nonarteritic anterior ischemic optic neuropathy: A PRISMA-compliant meta-analysis. Medicine (Baltimore), 2019. 98(46): p. e17861.
[16] A. Pahor and D. Pahor, [Development of Non-Arteritic Anterior Ischaemic Optic Neuropathy in the Initially Unaffected Fellow Eye in Patients Treated with Systemic Corticosteroids]. Klin Monbl Augenheilkd, 2017. 234(11): p. 1396-1403.

ISSN 2706-6819 Vol.4, Issue 10: 16-23, DOI: 10.25236/IJFM.2022.041004

[17] L. Li, Y. Su, J. Liu, and C. Chen, Efficacy of Vincamine treatment in a rat model of anterior ischemic optic neuropathy. Eur J Ophthalmol, 2021. 31(6): p. 3442-3449.
[18] M. A. Nguyen Ngo Le, Y. T. Wen, Y. C. Ho, K. Kapupara, and R. K. Tsai, Therapeutic Effects of Puerarin Against Anterior Ischemic Optic Neuropathy Through Antiapoptotic and Anti-Inflammatory Actions. Invest Ophthalmol Vis Sci, 2019. 60(10): p. 3481-3491.
[19] Q. Wang, S. Gao, Y. Luo, and Q. Y. Kang, Compound anisodine affects the proliferation and calcium overload of hypoxia-induced rat retinal progenitor cells and brain neural stem cells via the p-ERK1/2/HIF-1alpha/VEGF pathway. Exp Ther Med, 2017. 14(1): p. 600-608.
[20] W. Zhang, J. Zhao, C. Guo, X. Du, X. Yang, and C. Fang, Meta-analysis of the safety and effect of breviscapine combined with mecobalamin for diabetic peripheral neuropathy. Chinese Traditional Patent Medicine 2016. 38(5): p. 10 (in Chinese).
[21] A. M. Aftab, M. Iqbal, A. Rauf, and A. Ali, Non arteritic anterior ischemic optic neuropathy; does Anticoagulation help? J Ayub Med Coll Abbottabad, 2016. 28(4): p. 776-780.
[22] R. Foroozan, New Treatments for Nonarteritic Anterior Ischemic Optic Neuropathy. Neurol Clin, 2017. 35(1): p. 1-15.
[23] K. Dickersin and T. Li, Surgery for nonarteritic anterior ischemic optic neuropathy. Cochrane Database Syst Rev, 2015(3): p. CD001538.
[24] M. Soheilian, A. Koochek, S. Yazdani, and G. A. Peyman, Transvitreal optic neurotomy for nonarteritic anterior ischemic optic neuropathy. Retina, 2003. 23(5): p. 692-7.
[25] J. L. Bennett, S. Thomas, J. L. Olson, and N. Mandava, Treatment of nonarteritic anterior ischemic optic neuropathy with intravitreal bevacizumab. J Neuroophthalmol, 2007. 27(3): p. 238-40.
[26] V. P. Dave and R. R. Pappuru, An unusual presentation of nonarteritic ischemic optic neuropathy with subretinal fluid treated with intravitreal bevacizumab. Indian J Ophthalmol, 2016. 64(1): p. 87-8.
[27] D. B. Rootman, H. S. Gill, and E. A. Margolin, Intravitreal bevacizumab for the treatment of nonarteritic anterior ischemic optic neuropathy: a prospective trial. Eye (Lond), 2013. 27(4): p. 538-44.
[28] Y. Feng, P. V. LoGrasso, O. Defert, and R. Li, Rho Kinase (ROCK) Inhibitors and Their Therapeutic Potential. J Med Chem, 2016. 59(6): p. 2269-300.
[29] Z. A. Nizamudeen, L. Chakrabarti, and V. Sottile, Exposure to the ROCK inhibitor fasudil promotes gliogenesis of neural stem cells in vitro. Stem Cell Res, 2018. 28: p. 75-86.
[30] N. Sanjari et al., Intravitreal Injection of a Rho-Kinase Inhibitor (Fasudil) for Recent-Onset Nonarteritic Anterior Ischemic Optic Neuropathy. J Clin Pharmacol, 2016. 56(6): p. 749-53.
[31] S. Pankratova et al., Neuroprotective properties of a novel, non-haematopoietic agonist of the erythropoietin receptor. Brain, 2010. 133(Pt 8): p. 2281-94.
[32] M. Modarres et al., Intravitreal erythropoietin injection for the treatment of non-arteritic anterior ischaemic optic neuropathy. Br J Ophthalmol, 2011. 95(7): p. 992-5.
[33] T. N. Lin et al., 15d-prostaglandin J2 protects brain from ischemia-reperfusion injury. Arterioscler Thromb Vasc Biol, 2006. 26(3): p. 481-7.
[34] N. R. Miller, M. A. Johnson, T. Nolan, Y. Guo, A. M. Bernstein, and S. L. Bernstein, Sustained neuroprotection from a single intravitreal injection of PGJ(2) in a nonhuman primate model of nonarteritic anterior ischemic optic neuropathy. Invest Ophthalmol Vis Sci, 2014. 55(11): p. 7047-56.
[35] C. H. Chang, T. L. Huang, S. P. Huang, and R. K. Tsai, Neuroprotective effects of recombinant human granulocyte colony-stimulating factor (G-CSF) in a rat model of anterior ischemic optic neuropathy (rAION). Exp Eye Res, 2014. 118: p. 109-16.
[36] K. Abri Aghdam et al., Intravitreal Injection Of The Granulocyte-Colony Stimulating Factor For The Treatment Of Non-Arteritic Anterior Ischemic Optic Neuropathy: A Pilot Study. Semin Ophthalmol, 2021. 36(8): p. 649-657.
[37] Z. Ahmed et al., Ocular neuroprotection by siRNA targeting caspase-2. Cell Death Dis, 2011. 2: p. e173.
[38] E. C. Solano, D. J. Kornbrust, A. Beaudry, J. W. Foy, D. J. Schneider, and J. D. Thompson, Toxicological and pharmacokinetic properties of QPI-1007, a chemically modified synthetic siRNA targeting caspase 2 mRNA, following intravitreal injection. Nucleic Acid Ther, 2014. 24(4): p. 258-66.
[39] Y. S. Han et al., C-Met-Activated Mesenchymal Stem Cells Rescue Ischemic Damage via Interaction with Cellular Prion Protein. Cell Physiol Biochem, 2018. 46(5): p. 1835-1848.
[40] C. B. Liu et al., Human Umbilical Cord-Derived Mesenchymal Stromal Cells Improve Left Ventricular Function, Perfusion, and Remodeling in a Porcine Model of Chronic Myocardial Ischemia. Stem Cells Transl Med, 2016. 5(8): p. 1004-13.
[41] L. Li et al., Preconditioning of bone marrow-derived mesenchymal stromal cells by tetramethylpyrazine enhances cell migration and improves functional recovery after focal cerebral ischemia in rats. Stem Cell Res Ther, 2017. 8(1): p. 112.

ISSN 2706-6819 Vol.4, Issue 10: 16-23, DOI: 10.25236/IJFM.2022.041004

[42] B. Yu et al., Exosomes derived from MSCs ameliorate retinal laser injury partially by inhibition of MCP-1. Sci Rep, 2016. 6: p. 34562.
[43] Y. Xiao, F. Geng, G. Wang, X. Li, J. Zhu, and W. Zhu, Bone marrow-derived mesenchymal stem cells-derived exosomes prevent oligodendrocyte apoptosis through exosomal miR-134 by targeting caspase-8. J Cell Biochem, 2018.
[44] B. Yu, X. R. Li, and X. M. Zhang, Mesenchymal stem cell-derived extracellular vesicles as a new therapeutic strategy for ocular diseases. World J Stem Cells, 2020. 12(3): p. 178-187.
[45] D. Li and Y. Gong, A Promising Strategy for Non-Arteritic Anterior Ischemic Optic Neuropathy: Intravitreal Mesenchymal Stem Cell Exosome. Curr Stem Cell Res Ther, 2021. 16(2): p. 109-114.
[46] C. Merino-Gonzalez et al., Mesenchymal Stem Cell-Derived Extracellular Vesicles Promote Angiogenesis: Potencial Clinical Application. Front Physiol, 2016. 7: p. 24.
[47] B. Mead and S. Tomarev, Bone Marrow-Derived Mesenchymal Stem Cells-Derived Exosomes Promote Survival of Retinal Ganglion Cells Through miRNA-Dependent Mechanisms. Stem Cells Transl Med, 2017. 6(4): p. 1273-1285.
[48] Y. Song, J. Y. Min, L. Mao, and Y. Y. Gong, Microvasculature dropout detected by the optical coherence tomography angiography in nonarteritic anterior ischemic optic neuropathy. Lasers Surg Med, 2018. 50(3): p. 194-201.
[49] E. Moisseiev et al., Protective Effect of Intravitreal Administration of Exosomes Derived from Mesenchymal Stem Cells on Retinal Ischemia. Curr Eye Res, 2017. 42(10): p. 1358-1367.
[50] J. N. Weiss, S. Levy, and S. C. Benes, Stem Cell Ophthalmology Treatment Study: bone marrow derived stem cells in the treatment of non-arteritic ischemic optic neuropathy (NAION). Stem Cell Investig, 2017. 4: p. 94.
[51] A. Liu, X. Tan, and X. Liu, Efficacy of Puerarin injection combined with conventional western medicines in treatment of patients with early acute anterior ischemic optic neuropathy and its effects on hemorheology. Medical Journal of Chinese People's Healt, 2019. 31(8): p. 3 (in Chinese).
[52] P. K. Liu, Y. T. Wen, W. Lin, K. Kapupara, M. Tai, and R. K. Tsai, Neuroprotective effects of low-dose G-CSF plus meloxicam in a rat model of anterior ischemic optic neuropathy. Sci Rep, 2020. 10(1): p. 10351.
[53] Y. Liu, H. Tan, J. Ran, and F. Wan, Effect of Buqi Huoxue Huayu Tongluo recipe on visual acuity, visual field, hemodynamics and flash electro-retinogram in patients with non - arteritis anterior ischemic optic neuropathy of qi deficiency and blood stasis type. Hebei J TCM, 2020. 42(3): p. 6 (in Chinese).
[54] H. Yang and J. Han, Retrospective Research of 90 cases of TCM Syndrome and Treatment in Anterior Ischemir Optic Neuropathy. Journal of Liaoning University of Traditional Chinese Medicine, 2018. 020(005): p. 208-211 (in Chinese).
[55] Y. Wang, H. Guo, Z. Zhao, L. Yu, and P. Bai, Study on electroacupuncture along the visual conductive pathway for ocular cell apoptosis in anterior ischemic optic neuropathy. Chinese Acupuncture & Moxibustion, 2017. 37(8): p. 6 (in Chinese).
[56] Y. Su, H. Liu, Y. Guo, and Z. Du, Clinical observation on the treatment of ischemic optic neuropathy by acupuncture in Chinese medicine. Guide of China Medicine, 2019. 17(32): p. 1(in Chinese).
[57] D. Zhao, The Clinical Research into anterior ischemic optic neurpathy Treated with Modified Huoxue Tongluo Decoction. Henan Traditional Chinese Medicine, 2017. 37(6): p. 3(in Chinese).