· Original article ·

Therapeutic time window of nerve cells injury after retinal acute ischemia

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Abstract

• AIM: To observe the clinical effects of traditional Chinese medicine combined with Western medicine for acute retinal artery occlusion (RAO) after a long time onset and to evaluate the treatment time window.

• METHODS: This retrospective study included 14 cases (15 eyes) with acute RAO, who received a combined modality therapy for 30 days, including conventional treatment, integrating traditional Chinese medicine and nerve cells restoration. The clinical data of visual acuity after treating 7 days, 14 days, 30 days and visual field pre-therapy and post-treatment were analyzed and evaluated.

• RESULTS: Thirteen cases (14 eyes) completed 14 days treatment, 11 cases (12 eyes) completed 30 days treatment. 11 eyes of 15 eyes (73.33%) at 7 days, 11 eyes of 14 eyes (78.57%) at 14 days, 11 eyes of 12 eyes (91.67%) at 30 days respectively gained significant vision improvement after treatment. Vision increased significantly after 7 days' treatment compared with pre-therapy ($P < 0.01$). The vision also increased significantly after 14 days' treatment compared with 7 days' and after 30 days' treatment compared with 14 days' respectively ($P < 0.05$). 12 of 14 cases completed visual field (VF) examination, VF mean sensitivity after treatment had significant improvement than before treatment ($P < 0.05$).

• CONCLUSION: Synthetic therapies, including conventional treatment, integrating traditional Chinese medicine and nerve cells restoration are effective and available in RAO, especially when the retinal edema is exisent. So treatment opportunity should not be limited within 3 days of symptom onset instead of a longer time, even 60 days.

• KEYWORDS: retinal artery occlusion; therapeutic effect; treatment time window

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INTRODUCTION

The retina as a portion of cerebrum can caused irreversibility nerve cells death and severe reduction of visual function after a history of transient ischemic attacks of retina. The retinal artery is cohnheim's artery and feeds the inner retinal layers. The patient with central retina artery occlusion (CRAO) routinely relates a history of painless catastrophic visual loss occurring over a period of seconds. The visual acuity ranges between counting fingers or worse at the time of initial examination. Obstruction of the central retinal artery or its branches are not uncommon presentations to the ophthalmology department. The combined incidence of CRAO and branch retinal artery occlusion (BRAO) lies between 0.5‰ and 1.5‰ of initial ophthalmical outpatient visits. The visual prognosis of CRAO is poor with 61% of patients having a final visual acuity (VA) of 0.05 or worse[1]. This degree of severe visual impairment is associated with limitations in social functioning, poor mental health[2]. Most CRAOs are thought to be caused by thrombosis or embolism [3]. Hayreh *et al* reported on the reversibility of the fundoscopic, angiographic, electrophysiological and morphological findings after clamping of the CRAO in 63 Rhesus monkeys, and concluded that the retinal tolerance time was approximately 105 minutes. Significant visual recovery clinically has been reported up to 72 hours after the occlusive event, but out of this time treatments for patients were abandoned, and they losed their vision forever. Therefore it is very important to enforce prophase treatment effectually, but when the treatment time window is? The length of time that the human retina can tolerate the ischemia before irreversible damage occurs remains uncertain. Many patients spend their long time to get ophthalmology department because of lacking of realization of the retinal artery occlusion (RAO) or being limited condition to visit doctors' office promptly. So it is all important to persist in a long time to treat CRAO and BRAO. We adopted measures actively to RAO these years and acquired unexpected curative effect after treating 15 consecutive cases with CRAO and BRAO of symptom onset from 12 hours to 2 months. We persist in a long time to treat them and get a good therapeutic effect and present our experience using conventional treatments, integrating traditional Chinese medicine therapies in these cases.

Table 1 Clinical and demographic characteristics

Case	Diagnosis	Eye	Age	Gender	Onset of symptoms	Retina oedema	Onset VA
1	CRAO	L	66	Female	13 hours	Y	CF/10cm
2	CRAO	L	55	Male	2 months	N	CF/20cm
3	CRAO	R	56	Male	3 days	Y	HM//30cm
4	CRAO	R	49	Male	2 months	N	0.1
5	CRAO	R	60	Male	2 months	N	CF/10cm
6	CRAO	R	51	Female	1 day	Y	CF/20cm
7	BRAO	R	74	Female	1 day	Y	0.3
8	BRAO	L	41	Male	5 days	N	0.4
9	CRAO	R	58	Female	27 days	N	CF/20cm
	CRAO	L				Y	0.08
10	CRAO	L	51	Male	12 hours	Y	LP/20cm
11	CRAO	L	18	Male	14 days	Y	0.08
12	CRAO	L	75	Female	7 days	Y	LP/anterior eye
13	CRAO	L	35	Female	5 days	Y	CF/30cm
14	CRAO	L	59	Male	20 days	Y	HM/30cm

Table 2 Post-treatment 7 days', 14 days', 30 days' visual improvement information

Vision	7d(n=15)	14d(n=14)	30d(n=12)
Visual improvement	(11 eyes)73.33%	(11 eyes)78.57%	(11 eyes)91.67%
No change in vision	(4 eyes)26.67%	(3 eyes)21.43%	(1 eye)8.33%
Visual worsening	0%	0%	0%

MATERIALS AND METHODS

Materials Fourteen cases(15 eyes) with CRAO and BRAO were retrospectively reviewed, who were consecutively treated at our hospital from April 2004 to January 2009. Patients who had vasculitis or arteriovenous malformations were excluded. All patients were assessed by ophthalmologists who confirmed the diagnosis of acute CRAO or BRAO using standard clinical criteria of vision loss associated with an ipsilateral relative afferent pupillary defect and diffuse, pale swelling of the retina with a macular "cherry-red" spot and attenuation of retinal vessels by ophthalmoscopy.

Methods VA at presentation was measured by standard visual acuity chart for all patients whose VA in the affected eye was 0.01 or better. Patients with VA less than 0.01 in the affected eye were assessed on an ordinal categorical scale progressing from counting fingers (CF) to hand movement (HM), light perception (LP) and finally to no light perception (nLP). Visual field (VF) was checked at treatment initiation and treatment end by Octopus 101 campimeter. Fluorescein angiography was performed whenever possible. Demographic details and vascular risk factors on admission were recorded. All patients with CRAO and BRAO presenting to our department accepted hospitalization and were treated with sublingual Nitroglycerin, retrobulbar injection of Anisodamine Hydrochloride, carbogen inhalation, oral acetazolamide 500mg, intravenous drip of shuxuetong parenteral solution and Acetylglutamide injection, intramuscular injection of cobamamide, oral Chinese herbal drugs immediately. Statistics of VA results after treating 7, 14, 30 days and VFs pre-therapy and post-treatment were recorded.

Statistical Analysis Statistical analysis was performed with SPSS 11.0 statistical software. Data were expressed as mean ± SD. VA and VF were evaluated by Student's t-test and categorical variables by Chi-square test. For all tests two-sided $P < 0.05$ were considered statistically significant. Decimal acuity was converted to log MAR equivalent.

The visual outcome was defined as a one-line improvement in VA on chart for patients with initial VA of 0.1 or better. For patients with initial VA worse than 0.1 a improvement was considered to have occurred if VA increased 0.04 or VA improved from CF to 0.02 or better, from HM to CF, from LP to HM and from nLP to LP[9].

RESULTS

Demographic and Clinical Characteristics Demographic and clinical features of the 14 patients with CRAO or BRAO were summarized in Tables 1. 14 consecutive cases (15 eyes), including 8 males and 6 females, aged 18-74 years, were reviewed. The time to presentation of CRAO or BRAO was from 12 hours to 60 days of symptom onset. One of the cases with binocular CRAO were caused due to jaw joint injection of glucocorticoids.

Visual Acuity Outcome 13 cases (14 eyes) completed 14 days treatment, 11 cases (12 eyes) completed 30 days treatment. 11 eyes of 15 eyes (73.33%) at 7 days, 11 eyes of 14 eyes (78.57%) at 14 days, 11eyes of 12 eyes (91.67%) at 30 days respectively gained significant vision improvement after treatment. The vision increased significantly after 7 days' treatment compared with pre-therapy ($P < 0.01$). The vision also increased significantly after 14 days' treatment compared with 7 days and after 30 days' treatment compared with 14 days' respectively ($P < 0.05$, Table 2 and Figure 1). 10 eyes of 14

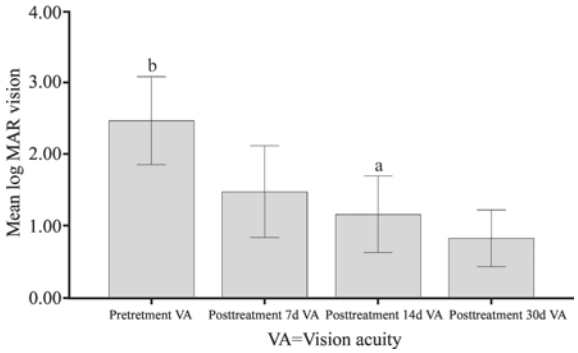

Figure 1 Pre-therapy and post-treatment visual results $^{b}P < 0.01$ *vs*Post-treatment 7,14,30 days; $^{a}P < 0.05$ *vs*Post-treatment 7,30 days.

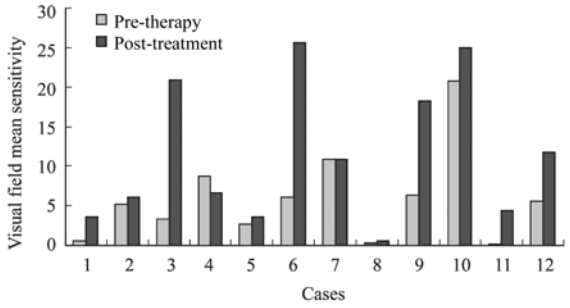

Figure 2 Pre-therapy and post-treatment visual field outcome comparison ($n=12$).

cases presented retinal edema or macular "cherry-red" spot when they visited our department first time. Vision of one of these patients with best vision improvement was from CF/10cm to 0.8. One of them with less vision improvement was from LP to 0.04. The retinal edema in 5 eyes already disappeared when they visited our department. Their vision increased less. Vision in 1 of 5 eyes improved 1 line,2 of 5 eyes from CF to 0.04 and to 0.08, 1 of 5 eyes from CF/20cm to CF/50cm.

Visual Field Outcome 12 of 14 cases completed examination of VF. Mean sensitivity (MS) of VF improved significantly at final treatment ($P<0.05$, Figure 2). The VA of 14 cases with CRAO and BRAO did not changed after follow-up of 6 months.

DISCUSSION

The therapies on RAO include conventional treatment (ocular massage, inhalation of carbogen, reducing intraocular pressure, expanding blood vessel), local intra-arterial fibrinolytic therapy[4] and transluminal Nd: YAG laser embolysis[5,6]. Clinical researches report of RAO aim directly at the time of 6 to 15 hours of symptom onset. 3 to 60 hours after acute reduction in vision was thought correct treatment opportunity commonly. So,when is the treatment time window of CRAO or BRAO? Results of animal models (rhesus monkeys) show retinal tolerance of ischaemia up to 3 hours. Hayreh *et al* evaluated the retinal tolerance time to acute ischemic insult in middle-aged or elderly rhesus monkeys with pre-existing atherosclerosis and arterial hypertension. Complete or almost total optic nerve atrophy and nerve fiber damage were presented in all eyes in which the duration of central retinal artery occlusion was 240 minutes or more. Some animals with stroke and good collaterals also will benefit from recanalisation after the three hour time limit,but benefit after six hours is exceptional[7]. Retina is impressible for local oxygen-poor. The earlier circulation is reestablished,the more visual function is recovered. It is likely that early recanalisation will preserve more retinal cells than late reperfusion.

It was complete artery occlusion after clamping of the CRA in 63 Rhesus monkeys. Different from the animal experiment, most CRAO in human being is incomplete clinically. So retina can tolerant a longer ischemia time. It was reported significant VA recover was possible within 3 days after the occlusive event. In our report the shortest time of symptom onset was 12 hours and the longest time was 60 days. All patients were managed actively by conventional treatment and integrating traditional Chinese medicine. Significant vision improvement of 73.33% at 7 days, 78.57% at 14 days, 91.67% at 30 days were found after our treatment. The visual function was recovering gradually along with time during treatment. It is clear that we should not adhere to traditional thoughts mode which treatment opportunity of CRAO or BRAO is within 1 to 3 days of symptom onset. It is never late to treat as long as the patient is not treated by ophthalmologist normally, even 60 days of symptom onset, to strive for more visual function recovery. Long enough time of treatment is also important. We find that visual function still continue to improve at 30 days after continuous treatment.

The retinal edema subsidises gradually after 4 to 6 weeks of RAO generally. 10 of 15 eyes presented retinal edema in our group when they visited our department. The VA of the 10 eyes were improved significantively. VA of the cases of retinal edema subsidised improved less. Retinal edema existence or not is valuable prognosis judgment index of RAO.

There have been some disputes on curative effect of conventional treatment. Some doctors maintain effectivity of the therapy,but most doctors view it as ineffective[8]. Several open-label clinical studies have suggested that local intra-arterial fibrinolysis (LIF) is efficacious in the treatment of central retinal artery occlusion[9-11], with up to 60% to 70% of treated subjects experiencing an improvement in VA. The time from onset of visual loss to LIF was 3 to 60 hours. The mean time was 12 hours. The treatment of acute thromboembolic CRAOs with LIF administered results in a better visual outcome a little than conventional therapy. Despite the efficacy of LIF in restoring VA in CRAO, concerns remain with its use in clinical practice. First, it is an invasive procedure that can cause embolic stroke (hemiparalysis, aphasia) and second, thrombolytic agents may result in either intracranial or systemic hemorrhages[12,13]. Treatment of transluminal Nd:YAG laser embolysis (NYE) aims directly at BRAO with visible emboli. Recent studies indicated that NYE treatment resulted in successful restoration of retinal blood flow and best-corrected visual acuity (BCVA). But complications such as vitreous hemorrhage and subretinal hemorrhage show up.

As yet, the aim of variety of reported management for CRAO and BRAO belonged to the cases with characteristics of short time after symptom onset is to increase the perfusion pressure of the retinal circulation, or to dislodge or lyse the obstructing thrombus/embolus. In fact, retina after its artery obstruction requires not only dredging blood vessel but also nerve cells restoration. Dredging blood vessel is the key, but the nerve cells nutrition and restoration can not be ignored. Dredging blood vessel and nerve cells nutrition and restoration were used in our cases. Retrobulbar injection of Anisodamine, sublingual nitroglycerin were executed at once after making a definite diagnosis of CROA or BROA. Following carbogen inhalation, intravenous drip of shuxuetong parenteral solution, traditional Chinese drug was taken. The treatments above aim to retinal artery recanalization. On the other hand, neurotrophy and restoration medicine were applied-intravenous drip of Aceglutamide, intramscular injection of Cobamamide. Aceglutamide can improve nerve cells metabolism and brain function, maintain nerves stress capability. Cobamamide can promote restoration of nerve injury. The formation principle of traditional Chinese drug is benefit for vital energy and dredging collaterals. Shuxuetong parenteral solution, which contains the extract of leech and lumbricus, executes the function of activating blood circulation to dissipate blood stasis and dredges the meridian passage. It is used to acute brain infarction clinically. Evident effect had been obtained by combined modality therapy above. It indicates the traditional Chinese medicine is effective to RAO and be worth of further study. The treatment time window of RAO needs to be delved as well.

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视网膜急性缺血后神经细胞损伤治疗的时间窗

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摘要

目的:观察中西医结合综合疗法治疗发病时间较长的视网膜动脉阻塞的临床疗效,并探讨视网膜动脉阻塞治疗的时间窗。

方法:采用常规疗法、联合中药、神经修复的综合方法治疗14例15眼连续就诊于中国中医科学院眼科医院一病区的患者,并对其进行回顾性研究,比较并分析治疗后7,14,30d视力结果及治疗前后视野结果。

结果:患者13例14眼完成14d治疗,11例12眼完成30d治疗。治疗7d后15眼中有11眼(73.33%)视力改善,14d后14眼中11眼(78.57%)视力改善,治疗30d后12眼中有11眼(91.67%)视力改善。治疗7d与治疗前比较($P<0.01$)、治疗14d与7d比较($P<0.05$)、治疗30d与14d比较($P<0.05$)视力均有显著的提高。14例中12例完成视野检查,治疗后视野平均敏感度较治疗前显著意义的改善($P<0.05$)。

结论:常规疗法、联合中药、神经修复的综合方法治疗视网膜动脉阻塞有较好疗效,尤其对发病后视网膜水肿未消失之前治疗价值更高,同时治疗时机也不应拘泥在传统概念的发病3d内,或许更长,比如60d。

关键词:视网膜动脉阻塞;治疗效果;治疗时间窗