

Original Article

Treatment of ethambutol-induced optic neuropathy by buqihuoxue formula combined with methycobal

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Received January 3, 2017; Accepted February 3, 2017; Epub April 15, 2017; Published April 30, 2017

Abstract: Tuberculosis is a common infectious disease in respiratory tract and frequently managed by ethambutol, which, however, can lead to toxic optic neuropathy under long-term therapy. Currently, the effective treatment for such complication is still lacked. This study aimed to investigate the treatment efficacy of combined therapy using both tradition Chinese medicine and drugs in treating such ethambutol-induced optic neuropathy (EON). A total of 38 patients diagnosed as toxic optic neuropathy after treating tuberculosis with ethambutol were recruited, and were sub-divided into combined therapy (Buqihuoxue Formula + Methycobal) and methycobal group. Vision was examined by Sellen's table, whilst color vision and fields were measured by Farnsworth-Munsell 100-Hue test and Humphrey 750i model, respectively. Optical coherence tomography (OCT) was performed to measure the thickness of retinal neural fiber layer. No significant difference existed in basic indexes between combined therapy and methycobal groups, whilst combined therapy had better efficacy. BCVA was elevated in all treatment groups, in which combined therapy had better efficacy. Methycobal and combined groups all significantly improved color vision, vision field and thickness of retinal fiber layer. Buqihuoxue formula, when combined with methycobal, had better efficacy in treating EON than single treatment.

Keywords: Buqihuoxue formula and methycobal, ethambutol, toxic optical neuropathy

Introduction

Tuberculosis is one common chronic respiratory duct disease in clinics and one of major public infectious diseases worldwide. Ethambutol is one first-line anti-tuberculosis drug and has been widely used in treatment [1]. However, ethambutol has certain toxicity, and may cause ethambutol-induced optic neuropathy (EON) in about 1% patients [2, 3]. EON onset usually has no regulation, but is correlated with patient age, drug time duration or dosage [4]. Previous study showed that the suspension of ethambutol can effectively retard further damage on optical nerves [5], whilst others believed that certain patients presented progressive damage of visions or even blindness even after suspending ethambutol [6]. Currently there is still no specific or large-sample study for EON treatment. Even though combined traditional Chinese and Western medicine has gained certain efficacy in treating optica nerve atrophy or optical neuropathy, no clinical study has been

performed targeting toxic optica neuropathy. The combined approach may provide novel ways for treating EON by integrating the whole-view and objective methods from both Chinese and Western medicine. Currently no systemic treating plan has been developed in treating EON by Chinese-Western combined approach. An optimized plan is thus required to combine both Chinese and Western medicine for clinical diagnosis and treatment of EON.

Patients and methods

Recruitment of research objects

A total of 38 patients were diagnosed as EON after taking ethambutol from October 2013 to August 2016 in Hangzhou Red Cross Hospital. Toxic optic neuropathy was diagnosed in tuberculosis patients taking ethambutol. Symptoms include blurred vision or sharp drop of vision, or loss of color discrimination. Clinical indexes included decrease of BCVA, suppressed color

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Table 1. General information of all research objects

Test index	Methycobal (18)	Combined therapy (20)	P value
Age (year)	67.43±12.31	65.54±10.32	0.61
Gender (M/F)	12/6	12/8	0.670
BMI	22.13±2.14	23.14±1.94	0.131
Blood pressure			
Systolic (mmHg)	135.35±13.54	134.21±14.87	0.810
Diabolic (mmHg)	87.32±9.43	86.95±8.34	0.898
Education level			
Junior school	3	4	0.960
High school	6	6	
College and above	9	10	
BCVA	0.33±0.12	0.30±0.14	0.485
Color vision (Normal/abnormal)	7/11	8/12	0.944
Average light sensitivity	15.02±3.21	14.12±2.78	0.360
Average thickness of RNFL (μm)	109.37±9.51	114.43±7.97	0.080

discrimination ability, vision field damage or lower RNFL. Other reasons that may cause optic neuropathy were ruled out. A time correlation existed between optic nerve injury and usage of ethambutol.

Exclusive criteria

Patients with optic neuropathy caused by other diseases, with severe tuberculosis or other organ lesions were excluded. Pregnant/lactating women, or patients with drug allergy history, complicated with other severe diseases that require further medication, or having mental disorder/unwillingness for trial, or those participating other clinical trials within one month were all excluded. EON patients were divided into Buqihuoxue formula combined with methycobal group (13 males and 7 females) and methycobal treatment group (13 males and 5 females). General information including age, sex, primary diagnosis time, averaged previous vision and corrected vision were recorded. All participants have signed informed consents of this study.

Treatment methods

Patients from both groups were treated for at least three months. Ophthalmology examination was performed 3 months after treatment. Buqihuoxue formula was modified from Sijunzi decoction and Liuweidihuang decoction, including 3 g ginseng, 6 g poria cocos, 9 g fried atracylodes rhizome, 9 g schisandra chinensis, 15 g

wolfberry, 15 g prepared radix rehmanniae, 15 g cornus officinalis, 15 g fried yam, 9 g americanwater plantain, 6 g cortex moutan, with selective addition/subtraction of plantain seed, 6 g Cynomorium songaricum Rupr or 6 g aconite. Methycobal was applied at 0.5 mg daily via intramuscular injection for 30 days, followed by 2 pills of methycobal for 30 days. Another 30 days of daily usage of 1 pill of methycobal followed depending on patient's conditions. The combined treatment group utilized both medications, whilst methycobal group received medication as described above.

Test assays

Best corrected visual acuity (BCVA) was measured by standard Sellen visual acuity table. Under ametropia, BCVA was measured again after correction. Color vision was described by Farnsworth-Munsell 100-Hue test apparatus (Macbeth Division of Kollmorgen, US). C-type standard illuminating light was tested on bilateral eyes. Vision field was measured by Humphrey 750i computerized vision field monitor for central and peripheral vision fields of center-30 and -60. Reliable parameters were strictly managed to minimize false positive rate less than 33% and loss of eye vision less than 20%. Vision field was reported by gray scale map to monitor light sensitivity of all points, average sensitivity, average deficits and false positive/negative rates. RNFL assay was performed to measure the thickness of retinal neural fiber layer (RNFL) by optical coherence tomography (OCT). Each participant received three circular scanning. All operations were performed by the same doctor to analyze RNFL thickness at upper, lower, nasal and temporal regions.

Evaluation of treatment efficacy

Patients were divided into three grades based on BCVA, color vision, RNFL and vision field. Significant efficient was defined as elevation of three or more indexes; Efficient was defined as two improved indexes. Inefficient was identified

Table 2. Comparison of treatment results

Group	Significant effect	Efficiency	Inefficient	P value
Methycobal	5	7	6	0.032
Combined treatment	14	4	2	

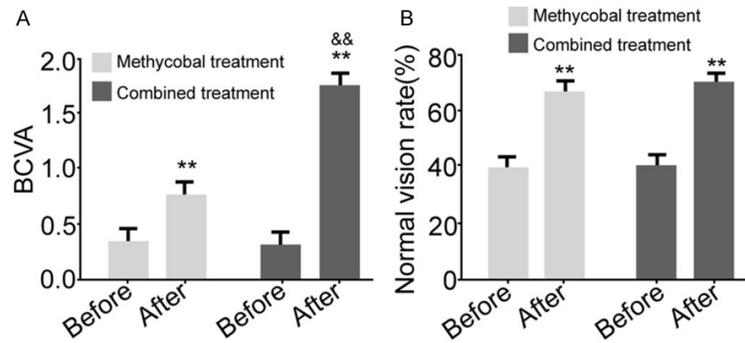


Figure 1. Comparison of BCVA and color perception before and after treatment. A. Treatment using methycobal only; B. Combined therapy using both Buqihuoxue formula and methycobal. **, P<0.05 comparing to those before treatment; &&, P<0.05 comparing to methycobal treatment group.

when one or no index was improved within 6-month follow-up. Compliance rate = total patient number receiving three-month treatment/(total patient number in each group-number of patients excluded) × 100%.

Statistical analysis

SPSS 16.0 statistics software was used for data analysis. Those fitted normal distribution were compared by random assigned student t-test. Those did not fit normal distribution were compared by rank-sum test. Enumeration data were compared by (corrected) chi-square test. The test significance was defined when α=0.05.

Results

Comparison of general information in all samples

Statistical analysis of both combined and methycobal treatment groups found no significant difference in all basic indexes, suggesting comparable parameters between two groups (P>0.05, **Table 1**).

Test result analysis after treatment

A total of 20 patients received Buqihuoxue formula plus methycobal and 18 cases received methycobal treatment. The evaluation of treat-

ment efficiency found better results in combined treatment group (P<0.05, **Table 2**).

Comparison of BCVA and color vision

All affected eyes were tested for BCVA using standard charts. BCVA before and after methycobal treatment were 0.33±0.12 and 0.76±0.15, respectively (P<0.05). BCVA before and after combined therapy were 0.30±0.14 and 1.75±0.13, respectively (P<0.05). These results suggested that all treatment methods could improve vision, with better efficiency in the combined approach (P<0.05).

Test of color discrimination showed that methycobal and combined group elevated normal color vision rate from 7/18 (38.9%) or 8/20 (40.0%) to 12/18 (66.7%) or 14/20 (70.0%), respectively, with significant improvement (P<0.05, **Figure 1**).

Vision field examination before and after treatment

Indexes related with vision field, including average light sensitivity, average deficiency and variance of loss were analyzed. Averaged light sensitivity represents arithmetical average value of light sensitivities among all test points. Averaged deficiency represented the difference between average light sensitivity in patients and in normal age-controlled people. Variation of loss was defined as non-homogenous deficient of vision field. Analytic results were shown in **Table 3**.

RNFL test results before and after drug treatment

OCT was used to measure RNFL thickness. Statistical analysis of results showed significantly elevated RNFL thickness in both lower and temporal quadrants of methycobal treatment group (P<0.05). In combined treatment group, RNFL in upper, lower and temporal quadrants were all higher than those in methycobal group (P<0.05, **Figure 2**).

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Table 3. Comparison of vision field test results before and after treatment

Test index	Methycobal treatment		Combined treatment	
	Before	After	Before	After
Averaged light sensitivity	15.02±3.21	10.21±2.18**	15.02±3.21	7.45±1.24**,&&
Average deficits	2.34±1.25	1.35±1.01	2.34±1.25	1.38±0.32
Variation loss	19.23±1.58	3.45±1.03**	19.23±1.58	3.25±0.45**

Note: **, P<0.05 compared to before treatment; &&, P<0.05 compared to methycobal group.

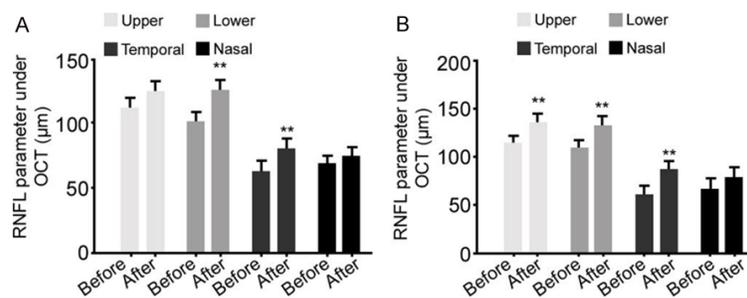


Figure 2. RNFL test results before and after drug treatment. A. Methycobal only; B. Buqihuoxue formula combined with methycobal. **, P<0.05 compared to before treatment.

Discussion

Toxic optic neuropathy is one group of vision dysfunction as a result of optic nerve injury induced by chemical reagent (including drugs) toxicity. Ethambutol is often used in tuberculosis patients, which frequently develop optic nerve toxicity [7-9]. This is possibly due to sufficient amounts of zinc in human eye tissues. Zinc is one important component of multiple enzymes in retina and optic nerve tissues. The intake of anti-tuberculosis drugs can deplete zinc ions, causing metabolic disorder and occurrence of drug-induced optical neuritis [10].

In one study performed on Korean people, the incidence of EON was 1.5% among all intakers of ethambutol, including certain eye abnormalities such as lower vision acuity (65.4%), abnormal vision field (65.4%) and vision dysfunction (61.5%) [11]. Vision field deficit or thinning of RNFL also frequently occurs in such kinds of toxicity [12, 13]. This study also revealed lower vision, abnormal vision field, and vision dysfunction, all of which are consistent with previous results. Methycobal is one important form of coenzyme as vitamin B12 derivative. Due to its high affinity for neural tissues, it has been widely applied in treating various neurological diseases [14]. Previous study has suggested

that vitamin B12 combined with methycobal significantly improved crush injury of optic nerve [15]. Most studies agreed that methycobal had treatment values for toxic optic neuropathy. This study also indicated improvement of eye vision and visual field after methycobal treatment.

With the development of Chinese medicine, it is believed that the combination of “activating blood and re-

solving stasis” theory in Chinese medicine and modern science can help to maintain normal visual functions under normal local blood circulation and nutrients. This study thus treated EON with Huoqibuxue formula and methycobal. Results showed better efficiency of combined treatment than single use of methycobal. Visual function, perception/vision field and thickness of RNFL were all improved under either combined treatment or methycobal. RNFL thickness is believed to be one important index evaluating eye disease [16]. For example, glaucoma patients may develop thinning of RNFL even at 6 years before symptom onset [17, 18], making it as one important index for multiple eye examinations [19, 20]. BCVA was also found to be better in combined group than that in methycobal group, with significant improvement of vision field, which has not been reported yet. Therefore, the combination between Buqihuoxue formula and methycobal to treat toxic neuropathy should be promoted in clinics to prevent unfavorable prognosis.

This study, however, only covered optic neuritis induced by ethambutol in tuberculosis patients, but not included those optic neuritis caused by other drugs or toxic, thus compromising representativeness of sampling. Meanwhile, due to lower incidence of EON, small sample size may

bias the interpretation. A larger-sample study thus is required for systemic evaluation of treatment efficiency.

Currently, no study has been performed regarding the combined treatment using both Buqihuoxue formula and methycobal against toxic neuropathy. Compared to traditional method using methycobal only, most indexes including visual acuity and vision field were all significantly improved in combined treatment group. Therefore, it is worth to promote such combined therapy in clinics to prevent the aggravation of toxic optic neuropathy.

Acknowledgements

This work was supported by Chinese medicine research program of Zhejiang province (No. 2015ZA145).

Disclosure of conflict of interest

None.

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