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STUDY PROTOCOL

Efficacy of intraorbital electroacupuncture for diabetic abducens nerve palsy: study protocol for a prospective single-center randomized controlled trial

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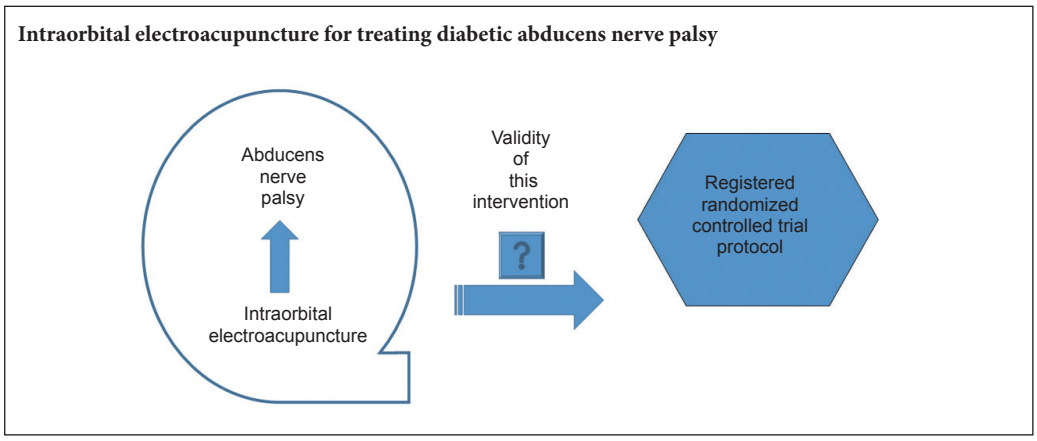
Graphical Abstract



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Abstract

Abducens nerve palsy (ANP) is commonly seen in patients with diabetes mellitus. The validity of acupuncture as a traditional Chinese medicine method in peripheral nerve repair is well established. However, its efficacy in randomized controlled trials remains unclear. Herein, we designed a protocol for a prospective, single-center, randomized controlled trial to investigate the effect of intraorbital electroacupuncture on diabetic ANP. We plan to recruit 60 patients with diabetic ANP, and randomly divide them into treatment and control groups. Patients in both groups will continue their glucose-lowering therapy. A neural nutrition drug will be given to both groups for six weeks. The treatment group will also receive intraorbital electroacupuncture therapy. We will assess efficacy of treatment, eyeball movement, diplopia deviation and the levels of fasting blood-glucose and glycosylated hemoglobin before treatment at 2, 4, and 6 weeks after treatment. The efficacy and recurrence will be investigated during follow-up (1 month after intervention). This protocol was registered at Chinese Clinical Trial Registry on 16 January 2015 (ChiCTR-IPR-15005836). This study was approved by the Ethics Committee of First Affiliated Hospital of Harbin Medical University of China (approval number: 201452). All protocols will be in accordance with *Declaration of Helsinki*, formulated by the World Medical Association. Written informed consent will be provided by participants. We envisage that the results of this clinical trial will provide evidence for promoting clinical use of this new therapy for management of ANP.

Key Words: *nerve regeneration; sixth cranial nerve; peripheral nerve injury; electroacupuncture; diabetes mellitus; eyeball movement; diplopia; rehabilitation; ocular motility disorder; intervention; randomized controlled trail; neural regeneration*

Introduction

The symptoms of abducens nerve palsy (ANP) consist of diplopia, strabismus and limitation or loss of the abduction function of the eyeball. Isolated ANP is seen in the majority of the cases, with an incidence of 11.3/100,000 (Patel, 2004). Pathogenesis is associated with a number of factors, although is predominantly related to nerve ischemia and hypoxia following microcirculation lesions (Goodwin, 2006; Akagi et al., 2008; Chi, 2009; Al-Bustani, 2015). Common causes of ANP include diabetes, cerebral infarction and atherosclerosis (Patel et al., 2005; Kinori et al., 2011; Sachdeva et al., 2013; Tamhankar et al., 2013).

The prevalence of diabetes in adult Chinese is currently 11.6%, and is progressively increasing (Yang et al., 2010; Xu et al., 2013). Interestingly, ANP was reported to occur in 29.6% of patients with diabetic ocular motor mononeuropathy (Greco et al., 2009). Indeed, the anatomical characteristics of the abducens nerve were also found to make it particularly vulnerable to hypoxia and ischemia (Hanson et al., 2004). The most common treatment for diabetic ANP consists of primary disease control, nerve nutrition and circulation improvement. For partial ANP patients, antagonistic muscle injection of botulinum toxin (Broniarczyk-Loba, et al., 2004; Sanjari et al., 2008), acupuncture (Do et al., 2014), acupoint injection therapy (Ren et al., 2008) and surgery may also be used (Phillips et al., 2007; Yurdakul et al., 2011).

Acupuncture is a widely used technique in traditional Chinese medicine, and has gradually been accepted worldwide, particularly for rehabilitation of peripheral neural regeneration and repair (He et al., 2015; Wong et al., 2016). However, the clinical use of acupuncture for ocular motor nerve repair is largely unstudied, and the mechanisms underlying neural regeneration are unclear.

The aim of the present study was to develop a protocol for investigating the therapeutic effect of intraorbital electroacupuncture for treatment of diabetic ANP. Diplopia deviation and eyeball movement were selected as the parameters used to evaluate differences between the control and treatment groups. This protocol represents the first registered randomized controlled trial for treating diabetic ANP. The intervention method is an innovation therapy, as the current option for this group of patients is waiting for endogenous recovery. Moreover, the therapeutic effect of this intervention is promising based on our pilot observational study. This protocol may be used to develop a new treatment option for patients with diabetic ANP.

Design and Methods

Participants

This study will be conducted in the First Affiliated Hospital of Harbin Medical University, China. We will enroll 60 unilateral diabetic ANP patients who visit our center. Patients will be randomized into the treatment and control groups. Patients in the control group will receive glucose-lowering therapy and oral vitamin B supplements. Patients in the treatment group will also receive intraorbital electroacupuncture. Measurement of eyeball movement and a computerized diplopia test will be performed in all patients (**Figure 1**).

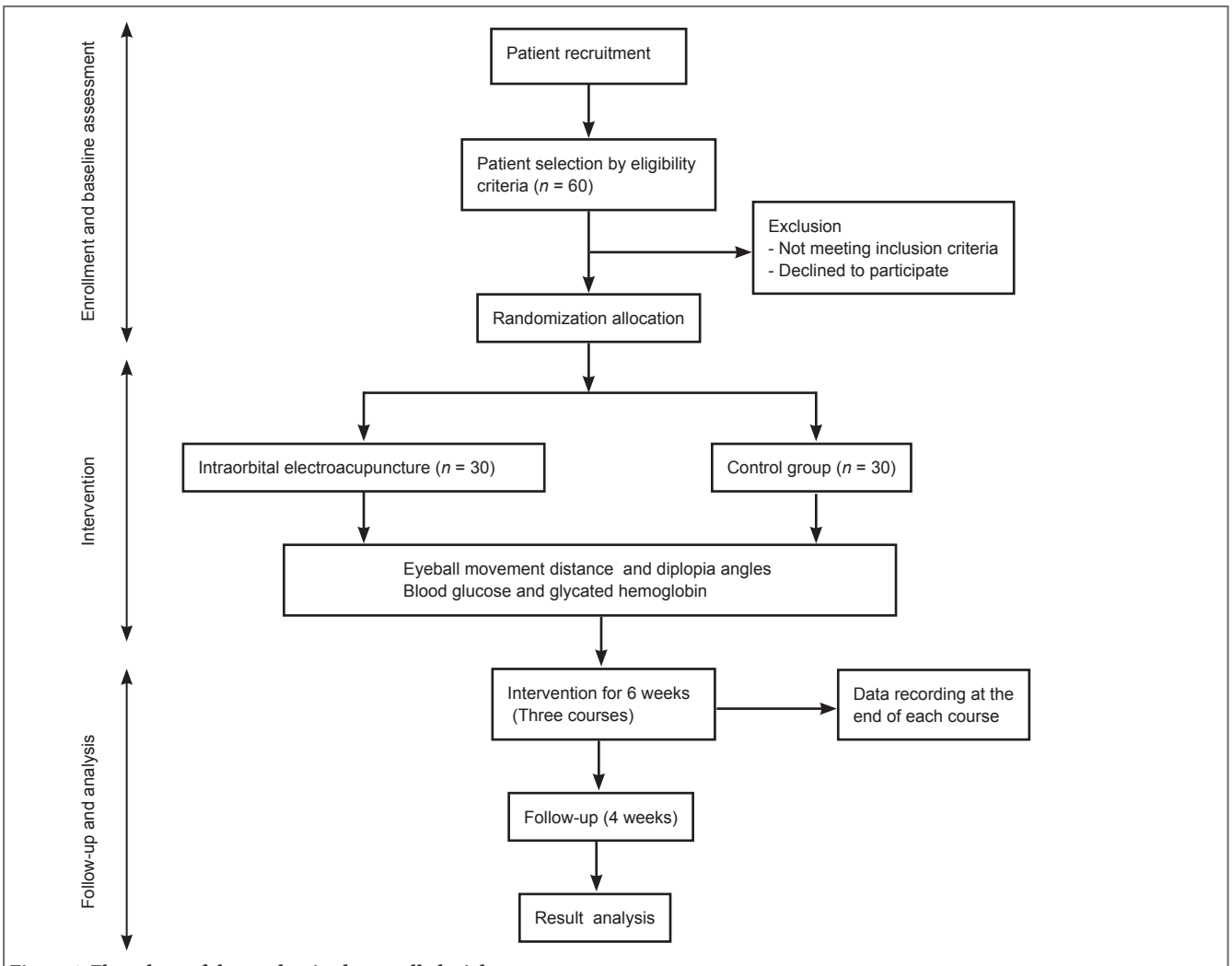

Figure 1 Flow chart of the randomized controlled trial.

The patients suffered from unilateral ANP. Based on the findings from neurology, endocrinology and ophthalmology tests, and the opinion of experts in these departments, the cause was identified as diabetes mellitus.

Inclusion criteria

Patients presenting with all of the following criteria will be considered for study inclusion.

- Confirmed diagnosis made by a neurologist or ophthalmologist
- Onset of ANP within one month (30 days or less)
- Age between 18–75 years without gender limitation
- Have not received medication or acupuncture intervention for ANP within seven days
- Willing to cooperate and voluntarily agree to participate and sign informed consent
- Controlled fasting blood glucose under 7 mM controlled glycosylated hemoglobin under 8% (Diabetes mellitus of Chinese medical association branch of learning, 2010; Lu et al., 2010)

Exclusion criteria

Patients with one or more of the following conditions will be excluded from this study.

- Other diagnosed medical conditions known to contribute to ANP symptoms, such as cerebral infarction, head trauma or thyroid disease
- Cannot complete a computerized diplopia test because of color blindness, hypochromatopsia or abnormal retinal correspondence
- Severe medical conditions that may limit their participation
- Severe infections in the eye or other sites
- Women who have a positive pregnancy test or who are planning to become pregnant during the study period
- Bleeding tendency, blood coagulation dysfunction or taking anticoagulant drugs
- Participating in other clinical trials that may affect our results

Withdrawal criteria

Patients presenting with one or more of the following conditions will be withdrawn from this study.

- Severe adverse reactions, such as optic nerve or eye injury
- Willing to quit
- Poor compliance

Sample size

Sample size will be determined by comparing the effective rate between the groups using random design. Using the effective rate (90% for intraorbital electroacupuncture *vs*. 50% for neural nutrition drug) in our pilot study, with a drop-out rate of 20%, our study should randomly recruit 30 patients (25 patients are needed, with an extra five patients for drop-out) to each group, which provides 90% power to detect a difference between means at a significance level of 5% with the use of a two-sided *t*-test.

Recruitment

We will recruit patients by sending leaflets, and setting out posters and advertisements around our hospital. The researchers will introduce the purpose and process of our trial to the patients. After providing informed consent, potential participants meeting the inclusion and exclusion criteria will be enrolled.

Randomization

The allocation of patients will be concealed using sequentially numbered, opaque and sealed envelopes. After an eligible patient is enrolled, the researcher will open the envelope to confirm the randomization assignment.

Blinding

The researcher responsible for outcome measurement and statistical analysis will be blinded during the trial. However, the participants and acupuncturists will not be blinded because of the nature of the intervention.

Interventions

Control group: Patients will receive 0.5 mg mecobalamin tablets (Eisai China Inc., Suzhou, China) three times per day. Intraorbital electroacupuncture: In addition to receiving the same interventions as the control group, patients will receive intraorbital electroacupuncture therapy. In brief, the patient will lie in the supine position. The skin of the lateral rectus projection area will be routinely disinfected. The eye ball will be gently pushed medially, while a 0.2 mm diameter and 25.0 mm long stainless steel needle (Huatuo, Suzhou, China) will be slowly inserted into the lateral rectus. The piercing depth will be approximately 20.0 mm, with four needles inserted intraorbitally and four needles inserted orbitally. An electric acupuncture apparatus will be used (Yingdi KWD-808 III; Changzhou Yingdi Electronic Medical Device Co., Ltd., Changzhou, China). Each group of electrodes (distinguished by different colored wires) will be used to generate 1.0–1.5 mA, 9 V, and 1.5 Hz currents for 40 minutes duration. One course of treatment will involve once daily stimulation, five times a week, for a total of ten times. Participants in both groups will continue to take their regular medications for glucose-lowering treatment.

Outcome measures

Primary outcome measure

Efficacy after the six-week intervention will be defined as: (i) Recovery – normal eye movement, diplopia symptoms disappear; (ii) Effective – improved eye movement distance and diplopia symptoms; and (iii) Invalidity – no significant changes in the eye movement distance or diplopia symptoms. Efficacy will be defined as the number of recovered patients + the number of effective patients / the total number of patients × 100%.

Secondary outcome measures

The secondary outcomes include the maximal horizon-

tal angle of diplopia deviations, difference value between the abducent distances for both eyes, visual acuity, fasting blood-glucose and glycosylated hemoglobin.

The maximal horizontal deviation of diplopia will be determined by a computerized diplopia test system. Patients will be tested at zero, two, four and six weeks. For each test, patients will control the mouse to finish the test by themselves. The software will automatically generate the maximal horizontal angle of diplopia deviation. The larger the value, the worse the condition of diplopia.

To minimize the measurement error, the difference value between the abducent distances for both eyes will be averaged from three independent assessors. The measurement will be performed at zero, two, four and six weeks. For each test, the assessor will ask the patient to turn his/her eyeball to the lateral side, and the distance between the center of pupil and the outer canthus for both eyes is then measured. The difference value will be calculated and recorded. A larger value represents weaker abducent function.

Visual acuity will be tested at zero, two, four and six weeks. Visual acuity will be measured using a logarithmic visual acuity chart, with a 5-m working distance (GB11533-89; Suhong Medical Equipment Co., Suzhou, Jiangsu Province, China). The visual acuity in logarithm of the minimum angle of resolution will be recorded.

The level of fasting blood-glucose will be tested at zero, two, four and six weeks. Blood samples will be taken and analyzed in the lab of the First Affiliated Hospital of Harbin Medical University, China. Samples will be taken in the morning, before the patients have eaten. The results of the test will be recorded.

The level of glycosylated hemoglobin will be tested at zero and six weeks. Blood samples will be taken and analyzed in the lab of the First Affiliated Hospital of Harbin Medical University. Samples will be taken in the morning, before the patients have eaten. The results of the test will be recorded.

All of these results will be used for the baseline comparison.

Adverse effects

We will monitor adverse events during the trial using a record sheet for each treatment. Unanticipated and undesirable events, including hematomas or nausea, will be recorded and managed. The final decision will be determined by the research leader (Zhou LY).

Data collection, management, analysis and open access

Data from all patients will be recorded in the case report form. To ensure the safety and reliability of the data, three observers will independently collect the data for difference value between the abducent distances and for visual acuity. The averaged data and other outcome results will be input into a computer and crosschecked by two investigators. All data will be managed through the clinical database of our hospital. Once the outcome results are input into the database, they can only be accessed by the research leader. After completion of the trial, the database will be sent to a statistician for analysis, who will provide a report of the results. The data will be sharing at ResMan within six months after the trial.

Data analysis

Continuous measurement data will be presented as means, standard deviations, medians and interquartiles. An independent statistician will analyze the data using statistical software (SPSS v19.0; IBM SPSS Statistics, IBM Co., Somers, NY, USA). A model-based analysis will be used to reduce bias in the case of patient drop-outs. Between-group changes in outcomes at zero, two, four and six weeks will be compared with repeated measures analysis of variance. A two-sided *P* value of less than 0.05 will be defined as statistical significance. Case and percentage will be used to represent the categorical data. We will test for potential interactions between treatment and covariates, such as age, gender, course of diabetes and severity of disease.

Trial Status

This study was registered on 16 January 2015. This trial is in the patient recruitment stage at the time of submission.

Discussion

ANP represents a type of ocular motor nerve palsy (Zhang et al., 2014). The causes of ANP are complex and diverse, although diabetes mellitus is a major factor (Tu et al., 2010). The main symptoms of ANP include eyeball movement disorder, strabismus and diplopia, which have serious effects on the quality of life and mental health of patients. A 13-year follow-up study showed that approximately 31% of ANP patients eventually had a relapse (Sanders et al., 2002). Currently, there is no effective intervention for the eye movement disorders and diplopia associated with ANP, and patients are typically informed to wait for endogenous neural repair (Galtrey et al., 2014). Thus, there is an urgent need to develop effective rehabilitation.

Although numerous observational studies suggest a therapeutic effect of acupuncture for treatment of ANP (Xiang et al., 2011; Zhou, et al., 2011; Liu and Hu, 2015), there are limited randomized controlled trial studies, and thus insufficient clinical evidence for promoting this treatment in daily practice. Further, the differences in efficacy between different acupuncture techniques are unknown. Thus, we designed this trial to investigate the efficacy of intraorbital electroacupuncture for treatment of ANP. Of note, because of the location of treatment, we will not use sham acupuncture as the control group. Further, the follow-up will only investigate the efficacy at one month after intervention. The efficacy of this therapy on other causes of ANP will also require further investigation.

In conclusion, this study may provide evidence for treating diabetic ANP with intraorbital electroacupuncture and for promoting its use in daily practice to reduce physical and mental discomfort in ANP patients.

Declaration of patient consent: *The authors certify that they will obtain all appropriate patient consent forms. In the form the patients will give their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.*
Author contributions: *LYZ, XML and TJL conceived and designed the protocol of this study, accomplished the draft of this manuscript and proofread the submission. MZ and CS participated to patient recruitment, baseline data collection and the manuscript preparation. XJJ, JCL and JYS evaluated the patients' efficacy and measured the patients' visual acuity, eyeball movement and diplopia deviation at different time points. All authors approved the final version of the paper.*
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