Effect of Lingqi Huangban granule plus intravitreal ranibizumab on macular edema induced by retinal vein occlusion: a randomized controlled clinical trial

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Abstract

OBJECTIVE: To investigate the effect of Lingqi Huangban granule (LQHB) plus intravitreal ranibizumab in the treatment of macular edema (ME) induced by retinal vein occlusion (RVO).

METHODS: A prospective, randomized controlled study was conducted. A total of 60 subjects with RVO induced ME were randomized into control group (CG) (30 eyes) and LQHB group (LQHBG) (30 eyes). CG patients underwent intravitreal ranibizumab (IVR) injections. LQHBG patients were treated with oral LQHB combined with IVR injections. In order to reduce the financial burden of the injections, we used one injection and pro re nata (PRN) regimen for both groups. The best-corrected visual acuity (BCVA), central macular thickness (CMT), and mean number of injections were evaluated at the beginning of treatment and 3, 6, 9 and 12 months afterward. All the subjects were followed up for 1 year.

RESULTS: At the beginning of treatment, there were no statistically significant differences between the two groups in terms of the general condition of patients (P > 0.05). At 3, 6, 9 and 12 months after treatment, however, the BCVA scores improved and the CMT measurements decreased in all patients (P < 0.05), with the improvement of LQHBG significantly greater than that of CG (P < 0.05). The mean numbers of ranibizumab injections were 1.8 ± 0.3 in LQHBG and 2.3 ± 0.6 in CG, respectively (P < 0.05). No adverse events were reported in both groups.

CONCLUSION: LQHB plus intravitreal ranibizumab could be a much more effective and economic treatment for stabilizing and improving vision with fewer intravitreal injections in the treatment of RVO induced ME. This integrative therapy appears to be a promising option for this type of patient.

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Keywords: Lingqi Huangban granule; Intravitreal injections; Ranibizumab; Macular edema; Retinal vein occlusion; Randomized controlled trial

INTRODUCTION

Retinal vein occlusion (RVO) is estimated to be the second most common cause of retinal vascular disease, after diabetic retinopathy.1 Macular edema (ME) that occurs as a result of central retinal vein occlusion (CRVO) or branch retinal vein occlusion (BRVO) leads to loss of vision in up to 5%-15% of BRVO cases and in almost all cases of CRVO.2 The pathogenesis of RVO induced ME is not completely understood, but
may result from a variety of factors, including hydrostatic effects from increased venous pressure, dysregulation of endothelial tight junctions, increases in the levels of inflammatory cytokines and vascular permeability factors. In recent years, as vascular endothelial growth factor (VEGF) was found to be the primary cause for ME, multiple studies that investigated the effects of several anti-VEGF agents in the treatment of RVO induced ME were conducted. Ranibizumab, a Fab fragment that binds all isoforms of VEGF-A, has been shown to markedly reduce RVO induced ME. However, repeated intravitreal injections are necessary to maintain vision improvement in a great number of cases. This entails disadvantages as there is an increase in the potential risks of complications, discomfort for the patients, and health care expenses.

In theory of Traditional Chinese Medicine (TCM), it is believed that the essence of RVO induced ME is a result of imbalances of Yin and Yang, which may result to visceral dysfunction. Qi stagnation and blood stasis of the eye fundus may finally result to the formation of edema. It is believed that medicine for invigorating the circulation of blood, thus inducing diuresis to alleviate edema should be taken. Lingqi Huangban granule (LQHB) is a compound Chinese herbal medicine of Shanghai General Hospital (Shanghai medicine system of word: Z05050795). The therapeutic effects of LQHB include strengthening Qi, nourishing liver and kidney, invigorating spleen to remove dampness, invigorating the circulation of blood, and remove obstruction from meridians.

This 1-year follow-up study was carried out on RVO-induced-ME patients with the treatment of LQHB plus intravitreal ranibizumab (IVR). This trial was at determining if this integrative therapy could achieve greater vision improvement than IVR treatment alone, and at the same time decrease the number of intravitreal injections.

MATERIALS AND METHODS

Source of cases
We conducted a prospective study of 60 patients with RVO induced ME at Ophthalmology Department of Shanghai General Hospital Affiliated to Shanghai Jiao Tong University from September 2015 through August 2017.

Criteria for diagnosis
The diagnosis was confirmed by fundus fluorescein angiography (FFA) (Heidelberg, Germany) and optical coherence tomography (OCT) (Zeiss, Germany) of the macular, whereby central macular thickness (CMT) was measured in microns. Best corrected visual acuity (BCVA) was recorded using Early Treatment Diabetic Retinopathy Study (ETDRS) chart at 4 m distance using a log MAR scale. Patients were included in the study if they met the following inclusion criteria:

- age, ≥ 18 years old;
- foveal center-involved RVO induced ME of less than 9 months duration;
- CMT, ≥ 250 μm;
- BCVA, 24-73 letters (20/40 to 20/320) in the study eye;
- initial diagnosis with no previous treatments, such as laser therapy or intravitreal injections.

Exclusion criteria
Patients were excluded from the study if one of the following occurred:

- presence of any other macular pathology, such as age-related macular degeneration (AMD) or diabetic retinopathy (DR) affecting the macular;
- concurrent serious diseases, such as cardiovascular diseases, liver or kidney diseases;
- prior anti-VEGF treatment or intraocular corticosteroid use in the study eye within 3 months;
- concern or doubt about treatment;
- known allergies to the ingredients of the medicine.

Ethical considerations
The study followed the ethical guidelines of the declaration of Helsinki. Written informed consent was obtained from each patient after provision of sufficient information about the procedures. The Institutional Review Board at Shanghai Jiao tong University Graduate School of Medicine approved this study.

Interventions
A total of 60 eyes in 60 patients were included. A computer-generated random number table was used. Patients were randomly divided into LQHB group (LQHBG, n = 30) or into control group (CG, n = 30) using the SAS 6.0 program (SAS, Inc., Cary, NC, USA). The trial statistician, who was not involved in the treatment schedule for the random allocation, generated the schedule for the random allocation sequence, which was held in a secure cabinet. Due to the nature of the interventions, it was not possible to blind the doctor who provided the treatments, or the patients who received the therapies. All patients were administered an initial dose of 0.5 mg (0.05 mL) ranibizumab (Lucentis; Genentech, South San Francisco, CA, USA) using the standard intravitreal injection procedure in a surgical room. Besides IVR injections, LQHBG patients were also orally administered with LQHB. LQHB was taken one pocket each time, twice a day immediately after a meal, for 12 months. In all patients with ischemic areas of the retina confirmed by FFA, laser photocoagulation (LPC) of the peripheral retina was done after the initial intravitreal treatment. In addition to the treatment medicines, usages of any other TCM or modern Western Medicine were prohibited.

Intravitreal injections
Topical anesthetic drops were given first, and a lid spec-
Statistical analysis was performed with SPSS 22.0.

Efficacy evaluation
Data about the duration of occlusion, previous eye diseases (interventions), existence of other systemic diseases was collected at the beginning of treatment. The ophthalmic examinations included determination of BCVA, intraocular pressure (IOP), anterior and posterior segment examination with indirect ophthalmoscopy and the findings of the fundus. The primary outcomes included the mean change from baseline of BCVA, the mean change from baseline of CMT as assessed by OCT, and the mean number of injections.

Follow-up visits were performed at 3, 6, 9 and 12 months afterward. At each visit, BCVAs were measured, whereas slit lamp examinations, IOP measurements, fundus examinations, OCT and FFA examinations were performed.

Statistical analysis
Statistical analysis was performed with SPSS 22.0 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY, USA). The quantitative data were expressed as mean ± standard deviation (x̄ ± s). Comparisons before and after treatment within each group were carried out with a paired t-test. Differences between groups were tested by t-test. A P-value of less than 0.05 was considered significant.

RESULTS

Patient demographics and baseline characteristics
A total of 60 eyes of 60 consecutive patients (28 men and 32 women) were analyzed. According to the experimental design, all patients were randomly divided into either LQHBG (n = 30) or CG (n = 30). None of the subjects in either group dropped out or were excluded. The study design is depicted in Figure 1. There was no statistically significant difference (P > 0.05) between the two groups in terms of gender (Female / Male), age, and average disease course (Table 1).

Changes in BCVA
At the beginning of treatment (0 month), there was no statistically significant difference between the two groups in terms of BCVA scores (t0 = 0.149, P0 = 0.433). At 3, 6, 9 and 12 months after treatment, the BCVA scores in the two groups increased, and the differences were statistically significant (t1 = 0.459, P1 = 0.011, t2 = 0.424, P2 = 0.019, t3 = 0.366, P3 = 0.047, t4 = 0.407, P4 = 0.026) (Figure 2).

Changes in CMT
At the beginning of treatment (0 month), there was no statistically significant difference between the two groups in terms of CMT measurements (t0 = 0.73, P0 = 0.471). At 3, 6, 9 and 12 months after treatment, the
CMT measurements in the two groups decreased, and the differences were statistically significant ($t_1 = 6.54$, $P_1 = 0.000$, $t_2 = 6.33$, $P_2 = 0.000$, $t_3 = 6.79$, $P_3 = 0.000$, $t_4 = 7.32$, $P_4 = 0.000$) (Figure 3).

**Average number of intravitreal injections**

The mean number of intravitreal injections of the patients with cure and effective efficacy was $1.8 \pm 0.3$ in LQHBG and $2.3 \pm 0.6$ in CG after a course of 1-year treatment, the difference between the two groups was statistically significant ($P < 0.05$).

**Safety**

During the clinical observation, no adverse events were noted in the two groups. There were no major ocular or systemic problems, such as increased intraocular pressure, retinal detachment, intraocular inflammation, or vascular events during the 1-year follow-up in both groups.

**DISCUSSION**

In recent years, studies have shown that intravitreal injections of the anti-VEGF agents are effective in reducing macular edema induced by RVO. However, repeated intravitreal injections are needed to maintain vision improvement, leading to greater potential risks of complications and expenses.

<table>
<thead>
<tr>
<th>Item</th>
<th>LQHBG ($n = 30$)</th>
<th>CG ($n = 30$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (female/male)</td>
<td>15/15</td>
<td>17/13</td>
</tr>
<tr>
<td>Age (years)</td>
<td>61.8±7.9</td>
<td>61.2±4.5</td>
</tr>
<tr>
<td>Duration of symptoms (months)</td>
<td>3.1±4.7</td>
<td>3.1±2.3</td>
</tr>
<tr>
<td>BCVA (letters)</td>
<td>47.8±8.0</td>
<td>48.4±9.9</td>
</tr>
<tr>
<td>CMT ($\mu m$)</td>
<td>387.0±24.6</td>
<td>384.3±26.6</td>
</tr>
</tbody>
</table>

Notes: CG: control group, intravitreal ranibizumab injections (1+ pro re nata); LQHBG: Linqi Huangban granule group, intravitreal ranibizumab injections (1+ pro re nata) combined with orally administered Linqi Huangban granule (one pocket each time, twice a day immediately after a meal, for 12 months); BCVA: best-corrected visual acuity; CMT: central macular thickness.
Our previous studies have shown that some TCM treatment combined with conventional treatment could have certain advantages.14,15 LQHB is a compound Chinese herbal medicine of Shanghai General Hospital (Shanghai medicine system of word: Z05050795). The main components include Danggui (Radix Angelicae Sinensis), Chuanxiong (Rhizoma Chuanxiong), Danshen (Radix Salviae Miltiorrhiza), Cangzhu (Rhizoma Atractyloidis Lanceae), Haizao (Tballus Sargassae Pallidi), Tuizi (Semen Cuscutae), Roucouongrong (Herba Cistanches Deserticoletae), Gouqizi (Fructus Lycii), etc. The therapeutic effect of LQHB is to strengthen Yang, nourish the liver and kidney, invigorate spleen to remove dampness, and remove obstruction from meridians.10 Previous studies have demonstrated that LQHB could obviously protect the blood circulation, inducing diuresis and nourishing the liver and kidney, while treating ME after IVR injection;14 Danggui (Radix Angelicae Sinensis), Chuanxiong (Rhizoma Chuanxiong) and Danshen (Radix Salviae Miltiorrhiza) work together to promote the blood circulation, repair the hypoxia damage of tissue and improve the obstruction of exudations;13 Cangzhu (Rhizoma Atractyloidis Lanceae) and Haizao (Tballus Sargassae Pallidi) nourish the spleen, thus inducing diuresis and alleviating macular edema;10 Tuizi (Semen Cuscutae), Roucouongrong (Herba Cistanche Deserticoletae), and Gouqizi (Fructus Lycii) supplement the liver and kidney, build the Yin, thus improving visual acuity.15

At 3, 6, 9, and 12 months after treatment, there were statistically significant differences between the two groups in terms of BCVA scores and CMT measurements, indicating that LQHB plus intravitreal ranibizumab may have significant therapeutic effect in treating RVO induced ME. Moreover, the combined treatment could also lead to fewer numbers of injections, with lower risks and less expenses. We also demonstrated that the safety of this treatment in LQHBG was same as that of CG group. None of the patients had adverse reaction.

In conclusion, LQHB plus intravitreal ranibizumab could be a more effective and economic therapy for stabilizing and improving vision with fewer intravitreal injections in the treatment of RVO induced ME. This integrative therapy may be a promising option for the patients.

REFERENCES

15 Lu BW, Wu XW. Retinal functional changes measured by microperimetry after intravitreal ranibizumab injection


