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ORIGINAL ARTICLE

The efficacy and safety of acupuncture combined with ranibizumab in the treatment of macular edema secondary to retinal vein occlusion

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Abstract

Background: Macular edema secondary to retinal vein occlusion (RVO-ME) impairs vision. Intravitreal ranibizumab is commonly used, but the adjunctive value of acupuncture remains unclear. **Objective:** To evaluate the clinical efficacy and safety of acupuncture combined with intravitreal ranibizumab injection for RVO-ME. **Methods:** Patients with RVO-ME (n = 45) were randomized into a control group (ranibizumab monotherapy) and an acupuncture group (ranibizumab and acupuncture). Both groups received monthly intravitreal ranibizumab (0.5 mg/0.05 mL) for 3 months, with a total follow-up of 6 months. Best-corrected visual acuity (BCVA), central macular thickness (CMT), macular vessel density (MVD) of superficial vascular complex (SVC), and deep vascular complex (DVC), foveal avascular zone (FAZ) area, and safety outcomes were assessed. **Results:** At 3 and 6 months post-treatment, BCVA, CMT, SVC-MVD, and DVC-MVD improved significantly in both groups (p<0.05). The acupuncture group showed significant reductions in SVC-FAZ and DVC-FAZ at 6 months (p<0.05), whereas the control group showed no such changes. Between-group differences at 6 months were significant for BCVA, CMT, DVC-MVD, and DVC-FAZ (p<0.05), with DVC-MVD differing significantly at 3 months (p<0.05). Adverse events (subconjunctival hemorrhage, elevated intraocular pressure, subcutaneous hemorrhage) were mild and comparable between groups (p>0.05). **Conclusion:** Acupuncture combined with ranibizumab effectively reduces RVO-ME, improves the microvascular structure of the macula, and is safe and reliable, with no serious adverse reactions. **Relevance for patients:** Patients with vision loss from RVO-ME may benefit from this combined treatment, which improves visual acuity, reduces retinal edema, and supports better long-term macular health with a favorable safety profile.

Keywords: Acupuncture; Ranibizumab injection; Retinal vein occlusion; Macular edema; Optical coherence tomography angiography

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1. Introduction

Retinal vein occlusion (RVO) is a common retinal vascular disease characterized by disrupted retinal vein circulation, increased vascular permeability, and macular edema (ME). ME is the primary cause of visual impairment in patients with RVO and is a prevalent cause of unilateral blindness, particularly in middle-aged and elderly individuals.[1] Persistent and recurrent ME can result in irreversible vision loss. Currently, the first-line treatment for ME secondary to RVO involves intravitreal injections of anti-vascular endothelial growth factor (VEGF) drugs. These treatments are known for their rapid effect and ease of administration, yet persistent and recurrent ME remains a frequent clinical challenge.[2,3] In traditional Chinese medicine (TCM), RVO is classified under the conditions of "sudden blindness" or "collateral damage sudden blindness." TCM suggests that the condition often arises from stagnation of qi and blood stasis, or from qi deficiency combined with blood stasis, leading to venous obstruction in the fundus and causing ischemia and edema in the retina and macula. Acupuncture, a core therapy in TCM, functions by unblocking meridians, promoting the flow of qi and blood, and restoring normal physiological function in blocked areas, aligning with the treatment principles for sudden blindness. This study aimed to observe the efficacy and safety of combining acupuncture with intravitreal ranibizumab injections in treating ME secondary to RVO.

2. Data and methods

2.1. Data

The clinical data of 45 patients (45 eyes) with RVO-ME admitted to the First Affiliated Hospital of Ningbo University from 2020 to 2023 were retrospectively analyzed and divided into the control group (26 cases, 26 eyes) and the acupuncture group (19 cases, 19 eyes), according to the treatment received. The control group included 12 males and 14 females, with a mean age of (57.38 ± 8.87) years. In the acupuncture group, there were 7 males and 12 females, with a mean age of (55.21 ± 9.98) years. This study was approved by the Ethics Committee of the First Affiliated Hospital of Ningbo University (Ethics batch number: 2023 Research No. 083RS-01). All patients provided written informed consent before participation in this study.

2.2. Inclusion and exclusion criteria

The patients were selected according to specific inclusion and exclusion criteria to ensure accurate assessment of RVO-ME:

Inclusion criteria: Patients with newly diagnosed RVO-ME meeting the 2019 Diagnostic and Treatment Guidelines for European Society of Retina Specialists Venous Obstruction,[4] confirmed through optical coherence tomography (OCT; Heidelberg Engineering, Germany).

Exclusion criteria: (i) Patients with diabetic retinopathy identified during post-mydriatic fundus examination; (ii) patients unable to cooperate with necessary examinations; (iii) history of glaucoma or uveitis; (iv) previous intraocular surgeries, such as cataract surgery, retinal photocoagulation, or vitrectomy, or cloudy refractive media. All participants and their families were informed about the study, and signed informed consent forms were obtained.

2.3. Methods

2.3.1. Control group

The control group received intraocular injections of ranibizumab. Specifications: 0.20 mL (10 mg/mL) per vial, registration number SJ20170004, manufactured by Novartis Pharma Schweiz AG, Switzerland. To prevent infection, levofloxacin eye drops were administered 3 times daily for 3 days before the procedure. During the procedure, the patient was placed in the supine position, and after achieving satisfactory topical anesthesia, the area was disinfected and covered with sterile drapes. The injection site was located 3.5 mm to 4.0 mm posterior to the temporal corneal limbus. A vertical injection was made into the sclera, delivering 0.5 mg/0.05 mL of ranibizumab. After the procedure, levofloxacin ointment was applied to the affected eye, which was then covered. This treatment was administered once a month for 3 months.

2.3.2. Acupuncture group

In addition to the treatments provided to the control group, the acupuncture group received acupuncture therapy. Local (eye) acupuncture points were primarily selected, with whole-body points included. Two to three point groups were chosen based on the patient's constitution and disease severity, with point selection rotated regularly. The body acupuncture points included *Jingming*, *Chengwei*, *Sibai*, *Touwei*, *Qiuhou*, *Guangming*, *Taichong*, *Zhaohai*, and *Sizhukong*. The technique used was mild reinforcing and attenuating, with needles retained for 30 min, once daily. Points were alternated, with 10 sessions constituting one course of treatment. Ear point pressure with the bean method, targeting Shen Gate, liver, spleen, kidney, and eye areas (Eye 1, Eye 2), was applied once daily for 10 sessions per treatment course. The treatment included a 3-day rest period, and a total of three courses were administered.

2.3.3. Examination methods and observation indicators

Before treatment, and at 3 and 6 months after treatment, best-corrected visual acuity (BCVA) was assessed using

a standard visual acuity chart and recorded as decimal acuity, and intraocular pressure (IOP) was measured with a non-contact tonometer. The same skilled ophthalmologist performed OCT examinations. Pupils were dilated to at least 5 mm for 30 min before the examination. Central macular thickness (CMT) was measured using OCT. A 3 mm × 3 mm section of the retinal macular area was scanned in OCT angiography (OCTA) mode, and foveal avascular zone (FAZ) images were obtained. The macular superficial and deep retinal blood flow charts were analyzed using ImageJ (version 1.52 p, National Institutes of Health, USA). Superficial vascular complex (SVC) macular vessel density (MVD) data were calculated for the FAZ area, and retinal MVD was measured at the deep vascular complex (DVC) level. Adverse reactions, including subconjunctival hemorrhage, elevated IOP, and subcutaneous hemorrhage, were assessed at 1, 3, and 6 months post-treatment.

2.4. Statistical analysis

All data were analyzed using the Statistical Package for the Social Sciences (25.0, IBM, United States). Variables were expressed as mean ± standard deviation. Paired-samples *t*-tests were used for intra-group comparisons, and one-way analysis of variance for comparisons between the two groups. The χ^2 test was used for count data. A value of $p<0.05$ was considered statistically significant.

3. Results

3.1. Baseline characteristics

The study included complete and consistent follow-up data for 45 patients (45 eyes), with 26 patients (26 eyes) in the control group and 19 patients (19 eyes) in the acupuncture group. There were no statistically significant differences between the two groups in terms of gender, age, disease duration, weight, or blood pressure ($p>0.05$), making the groups comparable, as shown in Table 1.

3.2. Visual, anatomical, and optical coherence tomography angiography outcomes

We compared BCVA, CMT, SVC-MVD, DVC-MVD, SVC-FAZ, and DVC-FAZ between the two patient groups. The BCVA, CMT, SVC-MVD, and DVC-MVD of the two groups showed significant improvement at 3 and 6 months after treatment compared to pre-treatment values ($p<0.05$). In the control group, there were no statistically significant differences in SVC-FAZ and DVC-FAZ between pre-treatment and 3 or 6 months post-treatment ($p>0.05$). Similarly, in the acupuncture group, no significant differences in SVC-FAZ and DVC-FAZ were observed between pre-treatment and 3 months post-treatment ($p>0.05$). However, both parameters showed statistically significant improvement at 6 months post-treatment ($p<0.05$). There were statistically significant differences between the two groups in BCVA, CMT, DVC-MVD, and DVC-FAZ at 6 months post-treatment ($p<0.05$). In contrast, at 3 months post-treatment, only DVC-MVD showed a significant difference between the groups ($p<0.05$), indicating that the deep blood flow density in the acupuncture group recovered more quickly than in the control group. Other indicators did not show significant differences between the groups. The results are shown in Table 2 and Figure 1.

3.3. Safety outcomes

There were no significant differences in adverse reactions between the two groups at 1, 3, and 6 months post-treatment, including subconjunctival hemorrhage, elevated IOP, and subcutaneous hemorrhage ($p>0.05$). Subconjunctival and subcutaneous hemorrhages fully resolved after a week of topical hot compress treatment, while patients with elevated IOP returned to normal after using anti-glaucoma eye drops. The results are shown in Table 3.

4. Discussion

Currently, integrated traditional Chinese and Western medicine is widely used in the clinical treatment of RVO, yielding positive results through classification, staging, and individualized treatment approaches.[5] In TCM, RVO is categorized as "sudden blindness," first described in Criteria for Syndrome and Treatment, Miscellaneous Diseases, Seven Tips. The pathogenesis is attributed to the combined effects of water retention and blood stasis.[6] In modern times, researchers have sought to verify acupuncture's actual clinical value and to clarify its physiological and biological mechanisms. Since the establishment of the World Federation of Acupuncture-Moxibustion Societies in 1987, acupuncture research has developed rapidly worldwide. The 1997 National Institutes of Health Consensus Conference on Acupuncture reviewed

Table 1. Comparison of demographic data between the two groups (mean±standard deviation)

Groups	Number of eyes	Gender (male/female)	Age (years)	Duration (days)	Weight (kg)	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)
Control group	26	12/14	57.38±8.87	27.04±25.86	61.19±10.80	137.58±19.63	83.65±8.21
Acupuncture group	19	7/12	55.21±9.98	22.00±23.54	65.95±11.44	136.16±16.76	85.79±9.41

Table 2. Comparison of BCVA, CMT, MVD, and FAZ between the two groups

Parameters	Control group			Acupuncture group			Comparison between groups at the same time point (*p*-value)	
	Before the treatment	After the treatment		Before the treatment	After the treatment			
		3 months	6 months		3 months	6 months	3 months	6 months
BCVA	0.32±0.15	0.50±0.22*	0.42±0.15*	0.36±0.19	0.59±0.25*	0.57±0.14*[a]	0.205	0.002
p-value		<0.001	<0.001		<0.001	<0.001		
CMT (μm)	376.62±77.44	268.15±30.83*	302.35±38.37*	407.58±75.29	289.32±50.88*	280.05±28.36*[a]	0.090	0.038
p-value		<0.001	<0.001		<0.001	<0.001		
SVC-MVD (%)	46.23±8.36	59.93±7.34*	52.65±7.39*	50.93±9.22	58.07±8.91*	57.21±8.20*	0.096	0.057
p-value		<0.001	<0.001		<0.001	<0.001		
DVC-MVD (%)	40.46±4.14	45.04±3.37*	43.91±3.03*	43.77±7.27	52.97±6.28*[a]	52.41±6.51*[a]	<0.001	<0.001
p-value		<0.001	<0.001		<0.001	<0.001		
SVC-FAZ (mm^2)	0.32±0.10	0.33±0.10	0.31±0.09	0.33±0.09	0.32±0.08	0.29±0.07*	0.773	0.480
p-value		0.496	0.152		0.237	0.012		
DVC-FAZ (mm^2)	0.29±0.11	0.30±0.10	0.29±0.08	0.28±0.04	0.27±0.05	0.25±0.04*[a]	0.203	0.049
p-value		0.165	0.753		0.300	*p*<0.001		

Notes: Data are expressed as mean±standard deviation. *p<0.05 versus before treatment within the same group; [a]p<0.05 versus the control group at the same time point.
Abbreviations: BVCA: Best-corrected visual acuity; CMT: Central macular thickness; DVC: Deep vascular complex; FAZ: Foveal avascular zone; MVD: Macular vessel density; SVC: Superficial vascular complex.

Table 3. Comparison of adverse reactions between the two groups

Adverse reaction (number of occurrences)	Control group (26 eyes)			Acupuncture group (19 eyes)		
	1 month (%)	3 months (%)	6 months (%)	1 month (%)	3 months (%)	6 months (%)
Subconjunctival hemorrhage	2 (7.69%)	1 (3.85%)	0 (0)	2 (10.53%)	2 (10.53)	0 (0)
Elevated IOP	1 (3.85%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Subcutaneous hemorrhage	0 (0)	0 (0)	0 (0)	2 (10.53%)	0 (0)	0 (0)

Abbreviation: IOP: Intraocular pressure.

the available scientific evidence and the therapy's efficacy for a wide range of disorders. Studies at that time focused largely on pain-related conditions and on the nature of meridians and acupoints, providing a firm foundation for the subsequent growth and acceptance of acupuncture.

Today, research interests have expanded well beyond pain control: In 2002, the World Health Organization listed 106 conditions for which acupuncture is indicated. Although some categories overlap, they are not identical.[7] The steadily accumulating evidence of benefit across diverse disorders has greatly advanced our understanding of this therapeutic approach.[8] By manually stimulating points along the meridians, acupuncture promotes the free flow of qi and blood and rebalances yin and yang.

Acupuncture treatment focuses on promoting blood circulation, removing blood stasis, and unblocking meridians. Wang and Kong[9] demonstrated that acupuncture combined with compound Xueshuantong significantly improves visual acuity in RVO patients with qi stagnation and blood stasis, and effectively regulates the expression levels of various cytokines in the body. Ranibizumab, a high-affinity recombinant monoclonal antibody fragment, inhibits neovascularization, reduces blood exudation, and promotes the absorption of edema, making it effective in treating RVO-ME.[10] It primarily promotes the absorption of intraretinal fluid and improves ME by inhibiting neovascularization, reducing vascular permeability, and regulating the permeability of the blood–retinal barrier through antagonistic mechanisms. Among these, ranibizumab is currently the most widely used anti-VEGF biologic agent. The 2010 European guidelines for the treatment of RVO recommend ranibizumab as a Grade A treatment for RVO-ME. Its overall efficacy, safety, and intravitreal injection route have been well-established in numerous studies.[11] However, the half-life of ranibizumab

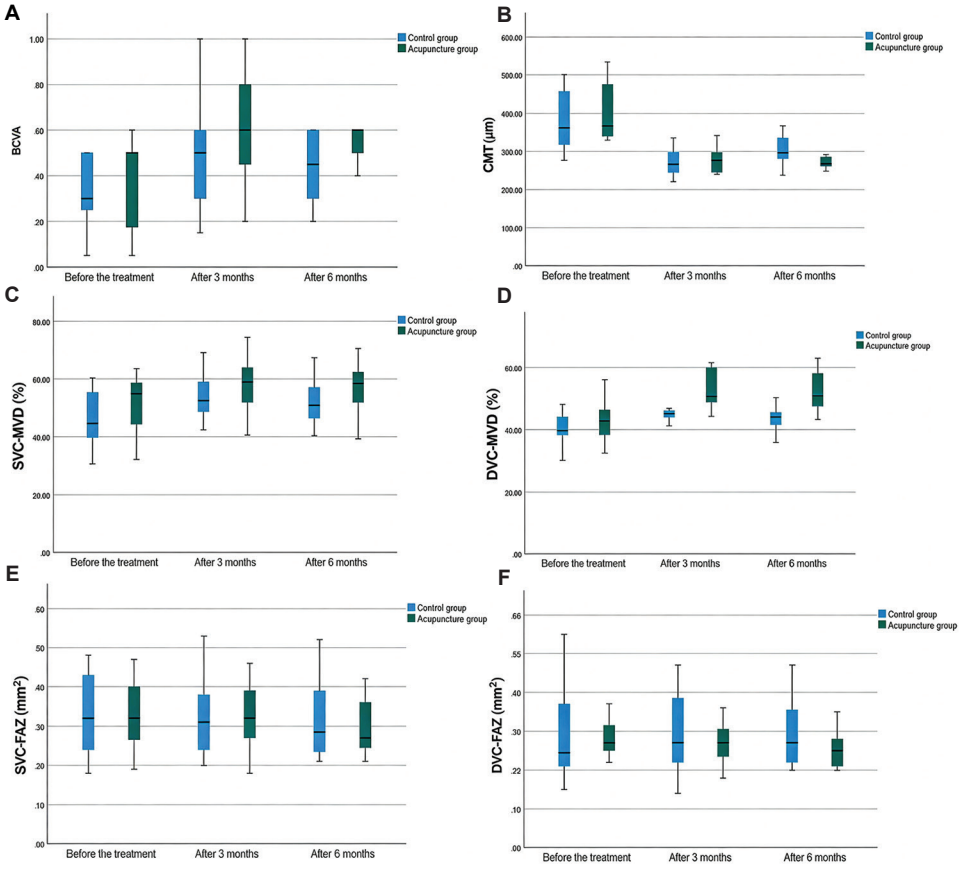

Figure 1. The box plot comparisons of (A) BCVA, (B) CMT, (C) SVC-MVD, (D) DVC-MVD, (E) SVC-FAZ, and (F) DVC-FAZ within-group (before and after treatment) and between the two groups
Note: *$p<0.05$.
Abbreviations: BVCA: Best-corrected visual acuity; CMT: Central macular thickness; DVC: Deep vascular complex; FAZ: Foveal avascular zone; MVD: Macular vessel density; SVC: Superficial vascular complex.

in the vitreous cavity is less than nine days, limiting its long-term efficacy. Studies show that on average, 8–9 injections are required annually. Due to ranibizumab's relatively short intravitreal half-life, repeated injections are required to sustain its therapeutic effect once the effective concentration declines. Data from pivotal trials show that monthly dosing for the first 6 months produces the maximal visual gain.[12] Thereafter, vision can be maintained with either monthly or *pro re nata* (PRN) injections, with no statistically significant difference between the two regimens. Consequently, a loading phase of 6 monthly injections followed by PRN retreatment (the "6 + PRN") is now regarded as the optimal anti-VEGF dosing strategy for RVO. This implies that every RVO patient should receive at least six injections, and on average, 8–9 ranibizumab injections are given within the first 12 months. Such frequent intravitreal injections not only carry the potential risk of endophthalmitis but also impose a significant financial burden on patients, limiting the widespread adoption of this therapy in China. The repeated intraocular injections increase the risk of cataracts, endophthalmitis, elevated IOP, and vitreous hemorrhage.[13,14] As a result, combining acupuncture with pharmacological treatment for RVO-ME has become a topic of increasing interest.

In this study, *Taichong* is selected as the source point of the liver meridian, while *Guangming* belongs to the gallbladder meridian. The combination of these two points, known as the *Yuan-Luo* acupoint pairing, helps regulate the liver and gallbladder, clear qi, promote blood circulation, and restore vitality. The combination of *Jingming* and *Sibai* helps to open the orifices and clear the eyes. *Chengqi*, which belongs to the stomach meridian of foot *Yangming*, works to dispel wind, clear heat, improve vision, and prevent tearing. *Qiuhou* is used to clear heat and enhance vision, while *Zhaohai* helps absorb heat and restore vitality. *Sizhukong* helps reduce turbidity and remove dampness. The combination of *Qiuhou* and *Guangming*, along with these other points, works to activate blood circulation and

improve vision. Auricular acupoint pressure therapy is an extension of auricular acupuncture. By stimulating specific points on the ear, it activates the body's bidirectional regulation functions, balances the qi in the eye meridians, and improves the local blood supply to the eyeball.

4.1. Efficacy outcomes and temporal dynamics

The results of this study showed that the acupuncture group experienced a statistically significant reduction in the FAZ area after 6 months of treatment, whereas the control group showed no significant change in the FAZ area before and after treatment. These findings remain a subject of debate,[15-17] with possible reasons for the discrepancies including differences in race, sample size, and measurement methods. Apart from the change in FAZ area, significant improvements were observed in other indicators before and after treatment in both groups, indicating that both ranibizumab intravitreal injection alone and the combination of acupuncture and medication were effective in treating RVO-ME. In a prospective case-series study,[9] 78 eyes with RVO attributed to qi stagnation and blood stasis were investigated. Control subjects received only oral compound xueshuantong capsules, whereas the intervention cohort received additional acupuncture treatment at *Touwei*, *Jingming*, *Chengqi*, *Sibai*, *Taichong*, and *Guangming*. The acupuncture-augmented regimen achieved a 97.4% clinical response rate and demonstrated significant superiority over monotherapy in visual function recovery and modulation of VEGF and serum endothelin-1 levels. These findings provide robust evidence that acupuncture is an effective adjunctive intervention for RVO and should be considered when standard pharmacotherapy alone proves insufficient. The improvement in DVC-MVD in the acupuncture group was significantly greater than in the control group at both 3 and 6 months after treatment. This may be attributed to acupuncture's ability to increase retinal blood flow and improve circulation,[18] possibly linked to glucocorticoids' effects on the DVC layer. Glucocorticoids may inhibit the production of inflammatory factors in this layer and help regulate the function of the blood–retinal barrier, contributing to similar improvements in visual function.[19] Regarding the underlying mechanisms, a previous study suggested that acupuncture stimulates parasympathetic nerve responses, thereby increasing choroidal and retinal blood flow,[20] whereas another study proposed that acupuncture inhibits sympathetic nervous system activity and raises endorphin levels to enhance retinal blood circulation.[21] When comparing other indicators between the two groups, the acupuncture group did not show significantly better results than the control group after 3 months of treatment, suggesting that acupuncture may not have an immediate effect on increasing retinal blood circulation. However, after 6 months of treatment, the differences became statistically significant, which may be due to the slower onset of acupuncture in treating RVO-ME. In a clinical trial evaluating the combined use of acupuncture and retinal laser photocoagulation for RVO,[22] visual acuities improved in both the treatment and control groups after 1 month, although the between-group difference did not achieve statistical significance. By the 6-month endpoint, however, the acupuncture-plus-laser cohort exhibited a significantly greater gain in BCVA than the laser-only controls ($p<0.05$). Parallel analyses of CMT revealed a statistically significant reduction in both arms. Nevertheless, the magnitude and velocity of CMT decrease were more pronounced in the acupuncture-augmented group, with the divergence becoming increasingly evident over time. Although the study did not incorporate pharmacotherapy, its longitudinal profile aligns with our observations: the therapeutic impact of acupuncture accumulates gradually, becoming demonstrably superior only after an extended observation period.

4.2. Hemodynamic-structural chronology and clinical implications

The temporal relationship between retinal hemodynamic alteration and microstructural injury remains a pivotal yet unresolved issue in the pathogenesis of retinal vascular disorders. Although glaucoma and RVO represent distinct clinical entities, they demonstrate remarkably similar perfusion anomalies—namely, reduced capillary density, patchy non-perfusion, and compromised blood–retinal barrier integrity—implying a shared "microcirculatory derangement–structural remodeling" cascade. Whether hemodynamic change precedes structural damage, or vice versa, is still vigorously debated. Several reports documented significant peripapillary vessel-density decline in glaucomatous eyes before any measurable alteration in retinal nerve fiber layer thickness,[23] whereas others observed prompt post-therapeutic rebound of flow density without concurrent change in macular ganglion-cell complex thickness, indirectly suggesting that vascular alteration antedates structural modification.[24] Conversely, another study argued that structural loss may precede detectable hemodynamic disturbances, proposing structural impairment as the primary driver of subsequent microvascular dysfunction.[25]

Optical coherence tomography angiography is a non-invasive imaging modality that enables high-speed scanning and layer-by-layer visualization of the retinal microvasculature, permitting quantitative assessment of retinal blood-flow parameters.[26,27] Previous investigations have demonstrated that eyes with RVO exhibit significantly reduced vessel density in both the

superficial capillary plexus (SCP) and the deep capillary plexus (DCP), accompanied by an enlargement of the FAZ.[27,28] In the present study, we longitudinally compared macular thickness and layer-specific vessel densities in both control and acupuncture-treated cohorts. Macular thickness decreased significantly in both groups within the early treatment phase; however, acupuncture eyes did not exhibit a measurable change in flow-density indices, such as FAZ area, until 6 months after initiation, implying that structural modification may precede hemodynamic improvement—a sequence that contradicts several previous observations. This finding not only expands the "flow-versus-structure" timeline debate but also provides fresh empirical evidence for clarifying microcirculation–tissue interactions across disparate retinal disorders. SVC-MVD and DVC-MVD in both groups were significantly improved at 3 and 6 months post-treatment compared to baseline (all $p<0.05$). Although there is no significant difference between the control and acupuncture group in SVC-MVD recovery, the acupuncture group demonstrated superior restoration of DVC-MVD. This divergence is presumably attributable to the vasoconstrictive effect of anti-VEGF agents. The pronounced impairment of the deep capillary layer may reflect the absence of pericytes and smooth-muscle cell coverage in the deep capillary plexus, rendering it more vulnerable than the superficial plexus.[29] Anti-VEGF can effectively alleviate leakage caused by SCP destruction, and disruption of DCP microcirculation may be a key factor for the persistence of ME after anti-VEGF treatment.[30] Consequently, we hypothesize that adjunctive acupuncture may exert a preferential protective effect on the retinal deep vascular network.

ME secondary to RVO is typically evaluated by the degree of macular thickening. However, if hemodynamic normalization is the inciting factor, early flow parameters may be more sensitive biomarkers to guide the timing and frequency of anti-VEGF therapy. On the other hand, should structural alteration precede vascular improvement, it implies that retinal tissue injury is already entrenched at baseline, mandating earlier neuroprotective or structural rescue strategies. Therefore, clarifying this chronology deepens our understanding of RVO pathobiology and furnishes a theoretical framework for individualized treatment algorithms centered on microvascular assessment. Our data further imply that early initiation of anti-VEGF therapy—followed by adjunctive acupuncture in later phases—may constitute a rational, sequential treatment paradigm for RVO-ME.

4.3. Safety profile and technique considerations

Needle withdrawal is the final step of an acupuncture treatment. Because it seems simple and technically undemanding, clinicians often pay little attention to it. In practice, however, numerous patients leave the couch with pain, bleeding, subcutaneous hematoma, or bruising; they become anxious and restless, and their satisfaction with acupuncture drops. These minor injuries are the most common complications of needling. A standardized withdrawal technique can greatly reduce discomfort and prevent conflict between doctors and patients. Research shows that the subcutaneous layer is rich in vessels and nerves.[31] If direction and digital pressure are ignored as the needle is pulled out, the tip or shaft can scrape the vessel wall or surrounding tissue; any additional force immediately increases pain and may further damage the vessel. Therefore, before the needle is removed, a sterile cotton swab is placed gently on the skin beside the puncture site. Pressure is light at first, so the skin is not dragged by the needle, and trauma is minimized. The needle is then slowly withdrawn back to the subcutaneous level against the line of insertion; pressure is increased slightly, and the shaft is briskly removed with one smooth, even motion, but not with excessive force. On the scalp and face, where vessels are denser than on the trunk or limbs, compression is maintained for a few extra seconds to limit bleeding. These simple measures reduce injury to vessels, nerves, and muscle, and they lessen post-treatment pain, bleeding, and bruising. Research suggests that subcutaneous hemorrhage can be absorbed by applying cold compresses within 48 h and hot compresses after 48 h.[32,33] Rare yet documented ocular complications of acupuncture include direct injury to the oculomotor nerve, manifesting as ptosis, mydriasis, and restricted extraocular motility, and to the optic nerve, resulting in sudden monocular blindness.[34] Imprecise needle angulation may traumatize the extraocular muscles, producing diplopia and gaze limitation.[35] Moreover, misdirection or inexperience can lead to globe perforation, retinal vessel rupture, intraocular hemorrhage, and even retinal detachment.[36] Systemic reactions have also been reported: approximately 10% of subjects experience intense anxiety or pain during periocular needling,[37] and arrhythmias, including atrial fibrillation. Given the anatomical vulnerability of the orbital region, clinicians must maintain continuous visual and verbal contact with the patient, employ pre-procedural counseling to mitigate apprehension, and be prepared to institute emergency measures should an adverse event occur.

Throughout the entire follow-up period, adverse events in both groups were limited to mild subconjunctival hemorrhage, subcutaneous hemorrhage, and transient IOP elevation; no severe anterior segment infection, vitreous hemorrhage, or systemic complications were observed. All hemorrhagic cases resolved completely within 1 week with local warm compresses, and IOP returned to baseline after

a single hypotensive eye drop. These findings indicate that adjunctive acupuncture therapy in addition to conventional anti-VEGF treatment does not pose additional safety risks and is well tolerated, meeting the safety requirements for further clinical dissemination. Although the bleeding entirely resolved after a week of hot compress treatment, this highlights the need for careful monitoring of patients' systemic conditions during acupuncture. It is essential to prevent potential bleeding, pay close attention to the technique and pressure applied during acupuncture, and avoid areas prone to bleeding to minimize the occurrence of adverse reactions.

5. Conclusion

Both acupuncture combined with ranibizumab and ranibizumab alone are effective treatments for patients with RVO-ME. However, compared to ranibizumab alone, the combination of acupuncture and medication more effectively reduces ME and improves the microvascular structure in the macular region, without causing serious adverse reactions, making it a safe and reliable option. Nevertheless, this study has several limitations. OCTA is not suitable for all patients with RVO-ME, as it requires clear refractive media and patient cooperation for accurate results. In addition, the sample size was relatively small (n = 45), which may limit statistical power and increase the risk of errors. The small cohort may affect the generalizability of our findings to the broader RVO-ME patient population. The follow-up duration was limited to 6 months, a relatively short period to assess the long-term efficacy and safety of the combined therapy. A longer observation period is needed to evaluate sustained treatment benefits and potential delayed adverse events. Future studies with larger sample sizes, multi-center collaboration, and extended follow-up periods are warranted to validate our results and improve external validity.

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Conflict of interest

The authors declare that they have no competing interests.

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Investigation: Yan Shi, Manhua Shi
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Ethics approval and consent to participate

All included patients provided their oral and written informed consent. The data of this study were published with the approval of the Ethics Committee of the First Affiliated Hospital of Ningbo University (Ethics batch number: 2023 Research No. 083RS-01).

Consent for publication

Written informed consent for publication was obtained from all participants.

Availability of data

All data included in this study are available upon request from the corresponding author.

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