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Evaluation of Ophthalmic Artery Branch Retrograde Intervention in the Treatment of Central Retinal Artery Occlusion (CRAO)

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Background: Central retinal artery occlusion (CRAO) is the occlusion of the central retinal artery resulting in retinal infarction and acute vision loss. Digital subtraction angiography (DSA)-guided superselective ophthalmic artery or selective carotid thrombolysis remains the preferred treatment method for CRAO. This study aimed to evaluate the safety and clinical efficacy of the novel ophthalmic artery branch retrograde thrombolytic intervention for CRAO.

Material/Methods: Fifty patients with monocular CRAO were enrolled, including 28 males and 22 females (mean age: 55.7 ± 2.3 years). The patients were randomly divided into two groups for thrombolysis with urokinase (400,000 U) and papaverine (30 mg) by either ophthalmic artery branch retrograde intervention (group A, n=26) or superselective ophthalmic artery/selective carotid intervention (group B, n=24). There was no significant difference in age ($P=0.58$), gender ratio ($P=0.49$), and time to onset ($P=1.00$) between the two groups. The adverse reactions and clinical efficacy were evaluated by postoperative DSA, fundus fluorescein angiography (FFA), and visual acuity tests.

Results: No serious complications, abnormal eye movement, or vitreous hemorrhage occurred in either group. DSA showed that group A had an effective rate (92.30%) comparable to that of group B (100%, $\chi^2=2.08$, $P=0.25$). FFA suggested that both groups had similar treatment efficacy ($\chi^2=3.09$, $P=0.21$). Visual acuity tests also confirmed a similar efficacy of the two intervention approaches ($\chi^2=0.25$, $P=0.88$).

Conclusions: The developed novel ophthalmic artery branch retrograde intervention is highly effective and safe for CRAO, and may be a superior method compared with the conventional approach.

MeSH Keywords: **Angiography, Digital Subtraction • Fluorescein Angiography • Retinal Artery Occlusion • Thrombolytic Therapy • Visual Acuity**

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Background

Central retinal artery occlusion (CRAO) is the occlusion of the central retinal artery resulting in infarction of the retina and acute, painless vision loss. The vision loss is often dramatic and permanent with poor prognosis of vision recovery. The incidence of CRAO is approximately 1.9/100,000 [1,2]. The majority of patients suffer profound monocular visual loss [3]. Furthermore, atherosclerosis-related thrombus, embolism, vasospasm, and giant cell arteritis have been known as causes of CRAO [4]. Since the disease is analogous to an ischemic cerebral stroke, the associated atherosclerotic risk factors may place CRAO patients at risk of future cerebral stroke and ischemic heart disease [5].

CRAO should be considered as an ocular emergency that should be treated without delay after symptom onset. Immediate hyperbaric oxygen (HBO₂) therapy has been used to supply oxygen to the ischemic retina in order to maintain viability while other treatment modalities are applied to restore the central retinal artery blood flow [4]. Traditional treatment modalities include ocular massage, anterior chamber paracentesis, intraocular pressure-lowering medications, and vasodilators, all of which are relatively ineffective [6,7]. In recent years, treatment modalities have been developed including delivery of thrombolytic agents by surgical approaches [8,9] and the removal of embolism by the Nd: YAG laser [10]. Currently, digital subtraction angiography (DSA)-guided superselective ophthalmic artery thrombolysis or selective carotid intervention remains the preferred treatment method for CRAO [11–15]. During the procedure, the DSA-guided catheter is inserted through the femoral artery and extended successively through the aorta, common carotid, and internal carotid artery to directly apply ophthalmic or carotid thrombolysis. Ophthalmic artery branch retrograde thrombolytic intervention, a novel surgical approach developed by our team, is achieved through the terminal branches of the ophthalmic artery. The approach does not involve large intracranial vessels and greatly simplifies the surgical procedure. In this study, the clinical efficacy and safety of the ophthalmic artery branch retrograde thrombolytic intervention and superselective ophthalmic artery thrombolysis/selective carotid intervention were compared in a group of CRAO patients in order to provide a basis for the wide application of the new therapeutic approach in clinical practice.

Material and Methods

Subjects

This study included a total of 50 patients with monocular CRAO [16] confirmed by fundus fluorescein angiography (FFA) who were hospitalized in the Department of Ophthalmology at

the Fourth Hospital of Xian between March 2000 and September 2015. Study subjects were selected based on the indications and contraindications of thrombolytic therapy in acute cerebral infarction [17]. Specifically, the following selection criteria were used: aged between 18 and 78 years, within 76 h after onset, blood pressure below 180/100 mm Hg (1 mm Hg=0.133 kPa), and normal prothrombin time, thrombin time, fibrinogen, and platelet counts. The exclusion criteria included computed tomography (CT)-confirmed intracranial bleeding; a history of intracranial hemorrhage, intracranial arteriovenous malformation, or aneurysm; intracranial surgery; head trauma or stroke with the past month; active gastrointestinal or urinary bleeding with the past 21 d; surgery within the past 14 d; ultrasound-confirmed cardiogenic emboli and carotid atherosclerotic plaque; and history of severe heart, lung, kidney, and liver disease. The study was approved by the Ethics Committee at the Fourth Hospital of Xian. All patients were required to sign the informed consent.

Grouping

The 50 patients were randomly divided into two groups: group A (n=26), who underwent ophthalmic artery branch retrograde thrombolytic intervention; and group B (n=24), who underwent superselective ophthalmic artery thrombolysis/selective carotid intervention. All patients were treated as an ophthalmic emergency. The blood pressure of all patients was controlled below 140/90 mm Hg before thrombolytic intervention. DSA-directed thrombolysis was applied as described below.

Ophthalmic artery branch retrograde thrombolytic intervention

In group A, the skin around the diseased eye was disinfected and the supraorbital nerve was blocked by an injection of 1% lidocaine. The skin below the medial canthus or above the supraorbital foramen was cut, and the supratrochlear or supraorbital artery was exposed by blunt dissection (Figure 1). Distal arterial blood flow was blocked, and the vascular wall was pierced by a sharp knife to insert a microcatheter with a guidewire (Figure 2). The guidewire was removed and 4 mL of the contrast agent iohexol 300 (National Drug registration No. H10970325, Yangtze River Pharmaceutical Group) was injected into the artery a speed of 1 mL/s through the microcatheter using a 1 mL injection syringe. The ophthalmic artery was examined by DSA to confirm the correct insertion of the microcatheter (Figure 3). A total amount of 400,000 U of urokinase and 30 mg of papaverine was pumped into the artery through a coaxial microcatheter using a micropump. The microcatheter was removed and the artery ligated. The surgery was completed after the skin was sutured. The patients were not required to rest in bed after the surgery.

Figure 1. The supratrochlear or supraorbital artery was exposed by blunt dissection.

Figure 2. A microcatheter with a guidewire was pierced through the blood vessel wall.

Superselective ophthalmic artery/selective carotid intervention

The patients in group B were subjected to total cerebral angiography using GE-Innova 41001Q in order to exclude intracranial aneurysms, arteriovenous malformations, and other diseases, and to determine subsequent intervention with superselective ophthalmic artery or selective carotid thrombolysis. The femoral artery in the groin area was punctured using the modified Seldinger technology. Briefly, the skin at the puncture site was disinfected, and the body part near the femoral artery was anesthetized by 2% lidocaine. A 2-mm incision was created, and the femoral artery was pierced by an arterial puncture needle. A guidewire was placed into the femoral artery in the right position, and a 5F arterial catheter sheath, cannula, and catheter were inserted sequentially through the aorta, common carotid, and internal carotid artery to reach the ophthalmic artery. A total amount of 8 mL and 6 mL of the contrast agent iohexol 300 was injected in the internal carotid and the external carotid, respectively, at a speed of 2 mL/s using a high-pressure syringe. A total amount of 400,000 U of urokinase and 30 mg of papaverine was pumped into the artery through a coaxial microcatheter using a micropump. The

Figure 3. A DSA image showing the ophthalmic artery and a clear ring around the eye, which confirms the proper insertion of the catheter.

catheter was removed and the wound was dressed. The patients were required to rest in bed and closely monitored for bleeding at the puncture site and cardiovascular abnormalities for 24 h after the surgery.

Determination of treatment outcome

The patients were followed up for 5 to 21 days (mean follow-up period: 16 days) to observe systemic and local adverse reactions, and to evaluate the clinical effects based on the following criteria: (1) An effective treatment was marked by a thickened ophthalmic artery and its branches, faster circulation, and a clear ring around the eye in postoperative DSA examination. (2) The mean arm-retina circulation time (A-Rct) was defined as the time elapsed when the fluorescein traveled from the ulnar vein to the retinal artery, and the circulation time from the retinal artery to the posterior pole peripheral retinal artery filling was named retinal artery-peripheral filling time. The A-Rct and retinal artery-peripheral filling time were measured by FFA [7,8] using a Topcon TRC-50EX fundus camera (Topcon, Tokyo, Japan) to assess the retinal blood circulation recovery based on the following criteria: markedly effective: A-Rct ≤ 15 s, and retinal artery-peripheral filling time of all branches of the central retinal artery ≤ 3 s; effective: A-Rct was between 16 and 20 s, and retinal artery-peripheral filling time of all branches of the central retinal artery was between 4 and 8 s; and invalid: A-Rct ≥ 21 s, and retinal artery-peripheral filling time of all branches of the central retinal artery ≥ 9 s. (3) A visual acuity test was performed using the semiquantitative scale “no light perception, light perception, counting

Table 1. General information of study subjects in the two groups.

	Group A (n=26)	Group B (n=24)	P
Age (years)	56.25±13.23	54.33±11.57	0.58
Gender (female %)	11 (42.31)	10 (41.77)	0.49
Time to onset (hours)	21.97±13.29	21.97±10.13	1.00

fingers, and hand motion,” and the quantitative scale “0.02, 0.05, 0.1, 0.12, 0.15, 0.2, 0.25...0.6” to evaluate the postoperative vision. The treatment was considered markedly effective when the postoperative vision was improved for 3 levels compared with the preoperative vision, effective in case of 2 levels of improvement, and invalid in case of 1 or 0 level of improvement.

Statistical analysis

All data were analyzed using SPSS 13.0 statistical software (SPSS Inc., Chicago, Illinois, USA). Data were expressed as mean ± standard deviation and compared by t-tests. Percentages were analyzed by χ^2 test. $P < 0.05$ was considered statistically different.

Results

General information on subjects

A total of 50 CRAO patients were selected in this study including 28 males and 22 females. The mean age was 55.7 years, and the average time to onset was 22 h (range: 8–76 h). Concurrent hypertension (140–180 mm Hg/80–100 mm Hg) and diabetes were reported in 37 cases and 1 case, respectively. None of the patients had any history of rheumatic disease, congenital heart disease, trauma, or infection. In the preoperative visual acuity test, there were 25 cases of no light perception, 18 of light perception, and 9 of hand motion. The intraocular pressure (IOP) ranged between 14 and 20 mm Hg with a mean IOP of 19 mm Hg. As shown in Table 1, there was no significant difference in age ($t=0.55$, $P=0.58$), gender ratio ($\chi^2=0.481$, $P=0.49$), and time to onset ($t=-0.001$, $P=1.00$) between the two groups.

Comparison of the safety of the two surgical approaches

Among the 26 cases in group A with the ophthalmic artery branch retrograde thrombolytic intervention, the catheter was successfully inserted through the supraorbital artery and the supratrochlear artery in 1 and 25 cases, respectively, as indicated by clear display of the ophthalmic artery in DSA examination. Neither the internal carotid artery nor the common

Figure 4. A DSA image showing the thickened ophthalmic artery and clearer ring around the eye.

carotid artery was displayed in DSA. The orbital skin wound healed well after the surgery. In group B, a patient developed intraoperative cerebral vasospasm and concurrent disturbance of consciousness, and recovered after prompt symptomatic treatment. The groin wound healed well. During the surgery and follow-up examination, serious complications such as hematoma at the incision site, intracranial hemorrhage, and cerebral embolism occurred in none of the patients in both groups. Abnormal eye movement or vitreous hemorrhage was observed in none of the patients.

Comparison of the efficacy of the two surgical approaches

Treatment outcome of the two groups was compared by postoperative DSA, FFA, and visual acuity tests. Effective treatment was indicated by the thickened ophthalmic artery and its branches, faster circulation, and a clear ring around the eye in postoperative DSA angiography. In group A, the ophthalmic artery branch retrograde thrombolytic intervention was effective in 92.3% of cases (Figure 4), which was comparable to that in group B ($\chi^2=2.08$, $P=0.25$) (Table 2). The pre- and post-operative FFA images are shown in Figure 5A–5C and Figure 6A–6C

Table 2. Comparison of Treatment outcome of the two groups by postoperative DSA, FFA, and visual acuity tests.

	Test	Group A (n=26)		Group B (n=24)		X ²	P
DSA, n (%)	Effective	24	(92.3%)	24	(100.0%)	2.08	0.25
	Invalid	2	(7.7%)	0			
FFA, n (%)	Markedly effective	17	(65.4%)	16	(66.7%)	3.09	0.21
	Effective	7	(26.9%)	6	(25.0%)		
	Invalid	2	(7.7%)	2	(8.3%)		
Visual acuity test, n (%)	Markedly effective	11	(42.3%)	10	(41.7%)	0.25	0.88

Figure 5. FFA images in group A before the surgery. (A) An FFA image showing posterior pole opacity, edema, and a cherry-red macular spot. (B) An FFA image at 48 s showing the retrograde filling of the occluded vessel. (C) An FFA image at 320 s showing disc staining and arterial segmental filling.

Figure 6. FFA images in group A after the surgery. (A) An FFA image showing improved retinal edema. (B) An FFA image at 13 s showing full retinal artery filling. (C) An FFA image at 17 s showing full filling of the retinal artery and vein.

(group A), and in Figure 7A–7C and Figure 8A–8C (group B). There was no significant difference in treatment efficacy between the two groups as indicated by FFA results ($\chi^2=3.09$, $P=0.21$) (Table 2). Furthermore, all patients underwent visual acuity testing after the surgery. In group A, the percentage of markedly effective, effective, and invalid treatment was 42.3%, 50%, and 7.7%, respectively, which was similar to that in group B (41.7%, 50%, and 8.3%, respectively) ($\chi^2=0.25$, $P=0.88$)

Discussion

The pathogenesis of CRAO is similar to that of cerebral stroke. It has been known that the optimal therapeutic time window of arterial thrombolysis for acute stroke is 4.5 hours after onset. In clinical situations, the thrombolytic treatment for CRAO is often delayed due to various preoperative examinations, preparation, and communication with patients' families. The mean time elapsed from CRAO onset to thrombolytic intervention is 12.78 hours, which is far beyond the optimal therapeutic time window [18].

Figure 7. FFA images in group B before the surgery. (A) An FFA image showing posterior pole opacity, edema, and a cherry-red macular spot. (B) An FFA image at 18 s showing the retrograde filling of the occluded vessel. (C) An FFA image at 22 s showing the retrograde filling of the occluded vessel.

Figure 8. FFA images in group B after the surgery. (A) An FFA image showing improved retinal edema. (B) An FFA image at 13 s showing retinal artery filling. (C) An FFA image at 17 s showing peripheral retinal arterial filling.

In the conventional DSA-guided superselective ophthalmic artery or selective carotid thrombolytic intervention, the catheter is sequentially extended through the aorta, common carotid, internal carotid artery, and ophthalmic artery, which might potentially cause arterial spasm, emboli shedding, postoperative aortic dissection, bleeding at the puncture site in the femoral artery, etc. Moreover, the thrombolytic drugs might induce intracranial bleeding of closed blood vessels in past lesions. The incidence rate of serious complications (such as transient ischemic attack, cerebral infarction, and cerebral hemorrhage) and other adverse events is approximately 4% and 37.1%, respectively [18–20]. In this study, a patient in group B developed intraoperative cerebral vasospasm and concurrent disturbance of consciousness, and recovered after prompt symptomatic treatment. Preoperative brain CT has become an important step to detect abnormalities such as intracranial hemorrhage, cerebromalacia, cerebral arteriovenous malformations, and intracranial aneurysms in order to prevent the occurrence of serious complications and adverse events. Nevertheless, the examination has delayed the surgery. Therefore, it is highly urgent to develop an intervention approach that involves neither large vessels in the body nor intracranial vessels to reduce the incidence rate of intra- and post-operative complications. Furthermore, preoperative brain CT is not necessary before such approach, which may allow prompt treatment within the optimal therapeutic time window of CRAO.

The ophthalmic artery branch retrograde intervention is a novel approach developed by our group, during which the catheter is extended from the supratrochlear or supraorbital artery to the ophthalmic artery for thrombolytic treatment. The path involved in this approach is less than 1/10 of that in conventional superselective ophthalmic artery or selective carotid intervention. As a result, the patients who undergo this approach are not at risk of complications associated with conventional intervention. More importantly, the intraoperative injection pressure of thrombolytic drug is slightly higher than the systolic pressure of the ophthalmic artery or internal carotid, which pushes the thrombolytic drug into the ophthalmic artery after the injection. Neither the catheter nor the thrombolytic drugs enter any intracranial vessels other than the ophthalmic artery. In our study, the ophthalmic artery was clearly displayed during DSA examination, whereas the common carotid artery and internal carotid artery were not illustrated. The patients in group A were not required to rest in bed after the surgery, and no systemic and local adverse complications occurred.

In this study, both treatments were effective as indicated by thickened ophthalmic artery, faster circulation, and a clear ring around the eye in postoperative DSA examination. Intra- or post-operative complications occurred in none of the patients in group A despite the fact that preoperative brain CT was not performed in group A, suggesting the high safety of

the developed ophthalmic artery branch retrograde approach. Therefore, the approach does not require the time-consuming preoperative brain CT, and may greatly reduce the time elapsed from onset of the disease to surgical intervention. As a reliable method to directly display the conditions of retinal circulation [16], FFA was used to evaluate the treatment efficacy for CRAO in this study. No significant difference in the improvement of retinal blood circulation and visual function was detected between the two groups, revealing similar effectiveness of both therapies in the treatment of CRAO.

During the ophthalmic artery branch retrograde intervention, the catheter can be inserted through the supraorbital or supratrochlear artery. Nevertheless, the supratrochlear artery is the preferred vessel because the success rate of catheter insertion is much higher compared with the supraorbital artery due to its stable position and larger size [21,22]. Although special microcatheters and guidewires are used to deliver the thrombolytic drugs in both intervention approaches, the required

length of microcatheters and guidewires in group A is much shorter compared with that in group B, which may largely reduce the treatment cost.

Conclusions

In summary, the novel ophthalmic artery branch retrograde thrombolytic intervention developed by our team is highly effective and safe in the treatment of CRAO, and may be an alternative method for the delivery of therapeutic drugs in retinal vascular occlusive diseases. Nevertheless, the surgeon should be well aware of the emergency nature of CRAO cases, because irreversible damage may occur in nerve fibers if the disease exceeds 240 minutes [23].

Conflict of interests

The author declare no conflict of interests.

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