ORIGINAL RESEARCH

Effect of Laser Panretinal Photocoagulation Combined with Lucentis on Long-Term Visual Acuity of Patients with Retinal Arterial Macroaneurysm

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ABSTRACT

Objective • To analyze the efficacy of laser panretinal photocoagulation in combination with Lucentis treatment on patients with retinal arterial macroaneurysm and investigate more effective novel therapy options to treat retinal arterial macroaneurysm.

Method • This study was conducted in the Pediatric department of Chongqing Aier Hospital between October 2016 and October 2020, and a total of 62 inpatients were enrolled for the study. Patients were randomly organized into two groups, an 'observation group' with patients receiving combinational treatment of laser panretinal photocoagulation and Lucentis, and a 'control group' with patients treated by only laser panretinal photocoagulation, were allotted. Though a comparative statistical analysis, the clinical outcomes and adverse effects on both groups, including their best corrected visual acuity, central macular thickness, intraocular pressure, and required number of laser treatments before and after treatments, were investigated. Also prognosis associated factors for patient's visual function, were analyzed.

Results • The clinical efficacy of the combinational treatment of laser panretinal photocoagulation and Lucentis was better than single laser panretinal photocoagulation treatment, accompanied by decreased incidence of adverse reactions ($P<.05$). For a combinational treatment, the observation group showed improved best corrected visual acuity and reduced central macular thickness and intraocular pressure, including fewer laser treatments ($P<.05$). Also, a better prognostic quality of life score; (measured as physical function, mental state, visual function, and social activity ability of patients), was observed for a combinational treatment than that of laser panretinal photocoagulation treatment ($P<.05$).

Conclusion • Laser panretinal photocoagulation combined with lucentis can deliver with reduced incidence of adverse effects compared to laser panretinal photocoagulation treatment and hence can more effectively contribute to retinal rehabilitation of patients with retinal arterial macroaneurysm. (*Altern Ther Health Med.* 2023;29(8):412-417).

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INTRODUCTION

Retinal arterial macroaneurysm (RAM) is a pervasive acquired retinal vascular abnormality in the elderly, and hypertension is the primary inducement for it.[1] According to the survey, RAM has an incidence of approximately 1 in 4500 people, especially in middle-aged and elderly (above 40 years of age) people, and its incidence is annually increasing slowly in recent years.[2,3] The main clinical and pathological manifestations of RAM include vision loss and blindness caused by subretinal hemorrhage and edema, and even occlusion of arteries and capillaries that will induce ischemic cerebral infarction and myocardial infarction, and endanger patients' lives in severe cases.[4,5] At the current stage, the pathogenesis of RAM remains unclear. Clinically, hereditary vascular structure destruction and acquired vascular injury in the hypertension environment cause its primary pathogenesis.[6] Timely and effective symptomatic treatment is the key to protecting the life, health and body function of patients with RAM. Currently, the most frequently adopted clinical therapy for RAM is panretinal photocoagulation.[7] However, in recent years, ongoing studies have pointed out the defects of laser therapy. For instance, a small amount of laser therapy on tumor occlusion is not effective enough, and additionally its repeated implementation may aggravate the continuous bleeding in the subretinal cavity and cause secondary injury to patients.[8] Also, some studies have

reported declining visual acuity after panretinal photocoagulation treatment.[9,10] Therefore, there is an urgent requirement for an effective way to address the adverse effects of panretinal photocoagulation.

Reportedly, anti-vascular endothelial growth factor (VEGF) drugs have delivered remarkable results in treating RAM and greatly improved the efficacy on patients.[11] Ranibizumab; as a brand name Lucentis (LU), is the second generation recombinant of humanized VEGF subtype monoclonal antibody fragment, which suppresses VEFG receptor binding by binding with VEGF-A and lowers endothelial cell activity and neovascularization.[12] In clinical practice, LU has achieved remarkable results as a therapy for various ocular vascular-associated diseases[13,14], but its role in RAM remains unclear. In studies by Stahl, Mitchell, and others, laser therapy combined with LU has demonstrated higher clinical efficacy on retinopathy and diabetic macular edema.[15,16] Therefore, we expect that, a combination of panretinal photocoagulation and LU might have a high application value for RAM.

At the current stage, there is no relevant research at home and abroad to confirm our conjecture yet. Therefore, this study analyzed the clinical efficacy of retinal therapy combined with LU on patients with RAM to offer new directions and ideas for future RAM therapy and reliable reference guidelines for the subsequent application of laser panretinal photocoagulation in combination with LU.

MATERIALS AND METHODS

Study subjects

Totally 62 patients with RAM admitted to Pediatric Department of Chongqing Aier Eye hospital between October 2016 and October 2020 were enrolled, and they were divided into observation group (Obs group) and control groups (Con group) according to the random number table method. The Obs group treated by laser panretinal photocoagulation combined with LU and the Con group treated by laser panretinal photocoagulation alone. The study was approved by the Ethics Committee of the Pediatric Department of Chongqing Aier Eye hospital (No. 2015091709), and all study subjects signed an informed consent form.

Inclusion criteria. Patients with hypertension, patients confirmed with RAM after examination in our hospital, patients whose fundus fluorescence angiography indicated early retinal aneurysms, patients whose optical coherence tomography showed deep retinal hemorrhage and increased central macular thickness (CMT), patients with the monocular disease, patients > 18 years old, and those with complete case data.

Exclusion criteria. Patients comorbid with other macular diseases or eye diseases, patients who had received intraocular surgery or anti-angiogenesis therapy within half a year before admission, patients during pregnancy or lactation, and patients with metabolic, immune or organ dysfunction.

Treatment methods

Laser panretinal photocoagulation: Before therapy, the pupil of the patient was fully dilated and placed under a panretinoscope. The parameters of laser instrument were set as follows: diameter: 200 μm; exposure time: 200 ms for all patients; power: 150-250 mW for the Obs group and 200-400 mW for the Con group. After one week, the tumor was photocoagulated with a diameter of 300 μm, an exposure time of 200 ms and a power of 150 mW. After 3-4 weeks, decision was made to decide whether to continue photocoagulation according to the tumor and retina. For a combinational treatment, each patient in the Obs group was injected with LU via intravitreal injection 2h after photocoagulation therapy. Tobramycin eye drops were applied to each patient at three days before therapy (6 times/day), and the lacrimal duct of the patient was washed with saline at one day before therapy. Eyes of the patient in a supine position were anesthetized with oxybuprocaine hydrochloride eye drops, and the conjunctival sac was washed with gentamicin. A syringe containing LU was inserted into eyeball vertically from 4mm at the corneal limbus, and LU (0.05 mL) was injected slowly in this way. After injection, patients' eyes were covered with tobradex from tobradex eye ointment and dressing, and applied with antibiotic eye drops four times a day for three consecutive days.

Clinical efficacy assessment

Markedly effective: Macular hemorrhage disappeared completely and there was no active hemorrhage in the tumor after therapy; effective: the range of macular hemorrhage and active hemorrhage of tumor decreased by over 50%; ineffective: none of the above criteria were met. Total effective rate was calculated as, Total effective rate = (the number of patients with markedly effective treatment + the number of patients with effective treatment) /the total number of patients × 100%.

Outcome measures

Clinical efficacy, adverse reactions during therapy, including patients' other conditions like; the best corrected visual acuity (BCVA), central macular thickness (CMT) and intraocular pressure in the two groups before therapy (T0), after 2 weeks of therapy (T1), 4 weeks of therapy (T2), 6 weeks of therapy (T3) and 8 weeks of therapy (T4), were analyzed for both groups. Numbers of laser therapy time used during treatments for both groups were counted, and all patients were followed up for 3 years. In addition, the changes in the visual function of all patients were evaluated and the quality of life of patients was analyzed by using the 'quality of life' scale which measures the quality of life for Chinese patients with visual impairment.[17] Also, associated factors for the prognosis of patients' visual function were analyzed.

Statistical analysis

This study adopted GraphPad Prism for statistical calculation and drawing. Enumeration data (%) were analyzed via the chi-square test. Measurement data were analyzed by the independent-samples *t* test, paired *t* test, and

variance analysis, and their post hoc test was carried out via the least significant difference (LSD). In addition, logistic regression was used for correlation analysis. Value of $P < .05$ suggests a remarkable difference.

RESULTS

Clinical baseline data

The two groups were not greatly different in clinical baseline data like age and gender (all $P > .05$, Table 1).

Comparison of clinical efficacy

The Obs group showed a notably higher total effective rate than the Con group (93.55% vs. 74.19%, $P < .05$, Table 2).

Comparative analysis of adverse reactions

The Obs group showed an incidence of adverse reactions of 3.23%, lower than that of the Con group (19.35%) ($P < .05$, Table 3). This shows that panretinal photocoagulation combined with LU for RAM has a higher safety profile.

Comparative analysis of BCVA

At T0, the two groups were not different in BCVA ($P > .05$). At T1, BCVA in both groups increased and reached the highest level at T4 ($P < .05$). BCVA in the Obs group was higher than that in the Con group at T1, T2, T3 and T4 (all $P < .05$), and the increase of BCVA during each time interval in the Obs group was also more remarkable than that in the Con group (all $P < .05$) (Table 4 and Figure 1).

Comparison of CMT

At T0, the two groups were not different in CMT ($P > .05$). At T1, CMT in both groups decreased and reached the lowest at T4 ($P < .05$). CMT in the Obs group was lower than that in the Con group at T2, T3 and T4 (all $P < .05$), and the decrease of CMT during each time interval in the Obs group was also more remarkable than that in the Con group (all $P < .05$) (Table 5 and Figure 2).

Comparison of intraocular pressure

At T0, the two groups were not different for intraocular pressure ($P > .05$). At T1, intraocular pressure in both groups decreased and reached the lowest at T4 ($P < .05$). Intraocular pressure in the Obs group was lower than that in the Con group at T1, T2, T3 and T4 (all $P < .05$), and the decrease of intraocular pressure during each time interval in the Obs group was more remarkable than that in the Con group (all $P < .05$) (Table 6 and Figure 3).

Comparison of required number of times of laser therapy

The Obs group experienced laser therapy (2.06 ± 0.51) times, less than that in the Con group [(4.26 ± 1.18) times] ($P < .05$, Figure 4).

Comparison of prognosis

During the 3-year follow-up, we successfully followed up 57 patients in the Obs group and 55 patients in the Con group. According to the investigation, no notable difference was found between the two groups in the number of people with unchanged visual acuity ($P > .05$), but the Obs group had more patients with improved visual acuity and less people with decreased visual acuity than the Con group (both

Table 1. Comparison of Clinical Baseline Data

	Observation group (n = 31)	Control group (n = 31)	t or χ^2	P value
Age	63.0 ± 8.9	62.4 ± 9.9	0.251	.803
Hypertension duration (years)	4.2 ± 1.8	4.3 ± 1.6	0.231	.818
Dilation diameter (μm)	161.57 ± 26.05	164.15 ± 26.06	0.390	.698
Gender			0.313	.576
Male *vs* female	10 *vs* 21	8 *vs* 23		
Diseased eye			0.065	.799
Left eye *vs* right eye	14 *vs* 17	15 *vs* 16		
Tumor location			0.261	.610
Temporal maxillary *vs* temporomandibular	15 *vs* 16	13 *vs* 18		
Family history of illness			0.350	.554
With *vs* without	1 *vs* 30	2 *vs* 29		
Smoking			0.369	.544
Yes *vs* no	8 *vs* 23	6 *vs* 25		
Drinking			0.130	.719
Yes *vs* no	4 *vs* 27	5 *vs* 26		
Living environment			0.295	.587
City *vs* country	20 *vs* 11	22 *vs* 9		
Nationality			1.016	.313
Han *vs* Minority	30 *vs* 1	31 *vs* 0		

Table 2. Comparison of clinical efficacy

	Markedly effective	Effective	Invalid	Total effective rate
Observation group (n = 31)	17 (54.84)	12 (38.71)	2 (6.45)	93.55%
Control group (n = 31)	10 (32.26)	13 (41.94)	8 (25.81)	74.19%
χ^2				4.292
P value				0.038*

Table 3. Comparison of the incidence of adverse reactions

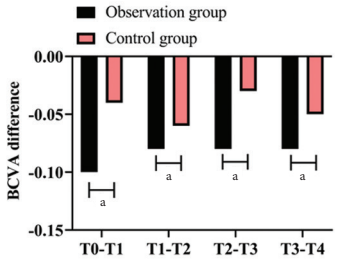
	Subconjunctival hemorrhage	Fundus hemorrhage	Severe pain	Dizziness and vomiting	The total incidence
Observation group (n=31)	0 (0.00)	1 (3.23)	0 (0.00)	0 (0.00)	3.23%
Control group (n=31)	2 (6.45)	2 (6.45)	1 (3.23)	1 (3.23)	19.35%
χ^2					4.026
P value					.045

Table 4. Comparison of BCVA

	T0	T1	T2	T3	T4	F	P value
Observation group (n = 31)	0.16 ± 0.08	0.26 ± 0.08[a]	0.33±0.10[a,b]	0.42 ± 0.13[a,b,c]	0.50 ± 0.09[a,b,c,d]	57.330	<.001
Control group (n = 31)	0.15 ± 0.06	0.19 ± 0.07[a]	0.25±0.09[a,b]	0.29 ± 0.09[a,b,c]	0.34 ± 0.10[a,b,c,d]	25.820	<.001
t	0.557	3.666	3.311	4.578	6.622		
P value	.580	<.001	.002	<.001	<.001		

[a]indicates difference with the situation at T0
[b]indicates difference with the situation at T1
[c]indicates difference with the situation at T2
[d]indicates difference with the situation at T3

Figure 1. Changes in BCVA difference.



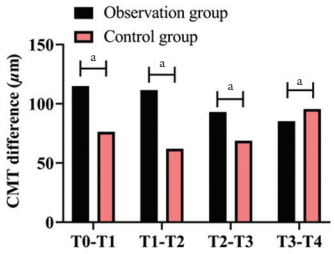
[a]$P < .05$

Table. 5 Comparison of CMT

	T0	T1	T2	T3	T4	F	*P* value
Observation group (n = 31)	644.82 ± 78.77	529.94 ± 94.36[a]	418.38 ± 103.79[a,b]	325.29 ± 104.70[a,b,c]	240.00 ± 115.54[a,b,c,d]	79.770	<.001
Control group (n = 31)	635.79 ± 94.76	559.49 ± 89.76[a]	497.42 ± 120.67[a,b]	428.66 ± 166.46[a,b,c]	333.03 ± 121.43[a,b,c,d]	28.540	<.001
t	0.408	1.263	2.765	2.927	3.090		
P value	.685	.211	.008	.005	.003		

[a]indicates difference with the situation at T0
[b]indicates difference with the situation at T1
[c]indicates difference with the situation at T2
[d]indicates difference with the situation at T3

Figure. 2 Changes in CMT difference.



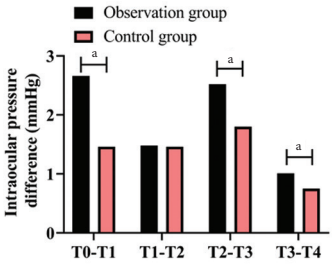
[a]*P* < .05

Table. 6 Comparison of intraocular pressure

	T0	T1	T2	T3	T4	F	*P* value
observation group (n = 31)	15.15 ± 1.57	12.48 ± 1.36[a]	11.00 ± 1.79[a,b]	8.47 ± 0.99[a,b,c]	7.46 ± 0.99[a,b,c,d]	156.600	<.001
control group (n = 31)	15.93 ± 2.05	14.47 ± 1.20[a]	13.01 ± 1.64[a,b]	11.21 ± 1.19[a,b,c]	10.47 ± 0.85[a,b,c,d]	75.310	<.001
t	1.682	6.109	4.610	9.855	12.840		
P value	.098	<.001	<.001	<.001	<.001		

[a]indicates difference with the situation at T0
[b]indicates difference with the situation at T1
[c]indicates difference with the situation at T2
[d]indicates difference with the situation at T3

Figure 3. Changes in intraocular pressure difference.



[a]*P* < .05

Table 7. Univariate analysis of factors affecting patients' visual function

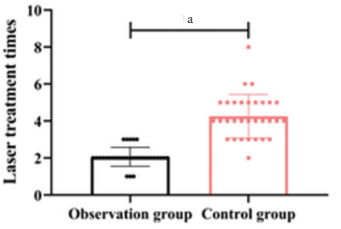
	Group A	Group B	t or χ^2	*P* value
Age	60.0 ± 7.6	75.8 ± 7.2	8.130	<.001
Hypertension duration (years)	3.9 ± 1.6	6.2 ± 0.9	6.806	<.001
Dilation diameter (μm)	155.35 ± 22.06	198.52 ± 15.29	8.711	<.001
BCVA after therapy	0.45 ± 0.11	0.24 ± 0.06	9.109	<.001
CMT after therapy(μm)	248.88 ± 105.28	476.46 ± 33.66	11.250	<.001
Intraocular pressure after therapy(mmHg)	8.59 ± 1.59	11.10 ± 0.95	7.356	<.001
Laser therapy times	2.8 ± 1.1	5.1 ± 1.5	6.619	<.001
Gender			2.715	.140
Male *vs* female	16 *vs* 32	1 *vs* 9		
Diseased eye			0.878	.349
Left eye *vs* right eye	21 *vs* 27	6 *vs* 4		
Tumor location			0.058	.810
Temporal maxillary *vs* temporomandibular	22 *vs* 26	5 *vs* 5		
Family history of illness			0.659	.417
With *vs* without	3 *vs* 45	0 *vs* 10		
Smoking			0.400	.527
Yes *vs* no	10 *vs* 38	3 *vs* 7		
Drinking			0.185	.667
Yes *vs* no	7 *vs* 41	2 *vs* 8		
Living environment			0.288	.592
City *vs* country	33 *vs* 15	6 *vs* 4		
Nationality			0.212	.645
Han *vs* Minority	47 *vs* 1	10 *vs* 0		

P < .05). In addition, the Obs group got notably higher life quality scores in physical function, mental state, visual function and social activity ability than that of Con group (*P* < .05) (Figure 5).

Univariate analysis of factors affecting patients' visual function

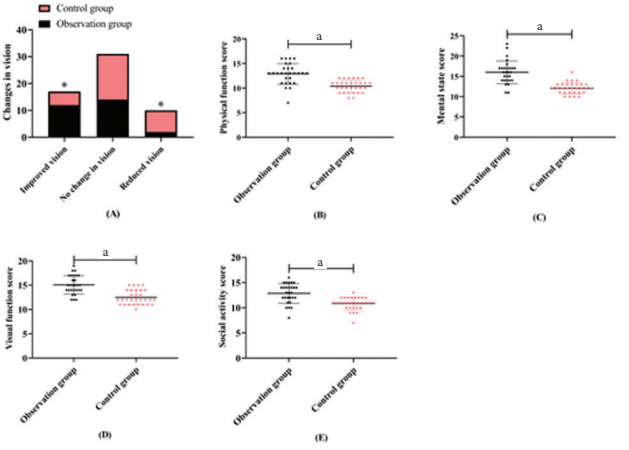
Patients with improved and unchanged visual acuity were assigned to Group A, and those with decreased visual acuity to Group B. Univariate analysis revealed that age, hypertension duration, dilation diameter, BCVA after therapy, CMT after therapy, intraocular pressure after therapy, laser therapy times and gender were all single factors impacting patients' visual function (all *P* < .05, Table 7).

Figure 4. Comparison of laser therapy times.



[a]*P* < .05

Figure. 5 Comparison of prognosis. (A) Visual acuity improvement. (B) Physical function score. (C) Mental state score. (D) Visual function score. (E) Social activity ability score.



[a]*P* < .05

Table 8. Multivariate analysis of factors impacting patients' visual function

	β	SE	Wald χ^2	*P* value	OR	95%CI
Age	0.005	0.067	0.12	.542	0.954	0.842-1.152
Hypertension duration	0.334	0.384	0.874	.142	0.724	0.354-1.624
Dilation diameter	3.842	1.142	7.426	.003	7.624	2.842-22.922
BCVA after therapy	0.142	0.251	12.621	<.001	0.741	0.242-2.812
CMT after therapy	0.642	0.148	21.620	<.001	1.942	1.324-2.842
Intraocular pressure after therapy	16.542	3.426	18.062	<.001	4.631	2.642-10.527
Laser therapy times	2.812	1.542	8.423	<.001	1.624	0.712-2.556

Multivariate analysis of factors impacting patients' visual function

Substituting the indicators with differences in the above analysis into SPSS and performing Logistic regression analysis, results presented that, age, hypertension duration, laser therapy times and gender were not independent factors for patients' visual function (all $P > .05$), while dilation diameter, BCVA after therapy, CMT after therapy and intraocular pressure after therapy were independent factors for it (all $P < .05$, Table 8).

DISCUSSION

At the current stage, the specific pathogenesis of RAM is not fully understood. Various congenital and acquired factors are believed to be strongly associated with this arterial wall disease.[18] Approximately 10%-20% of patients with RAM can recover spontaneously, but those with vascular leakage and retinal edema must be treated on time.[19] With the stable and remarkable effect unanimously recognized in clinical practice, laser photocoagulation is the first treatment of choice for RAM.[20] Precisely because of this, the research on RAM at home and abroad has stagnated, and with no new associated research going on for a long time, the clinical efficacy of laser therapy is limited. Moreover, we found over 20% of patients with RAM suffered impaired vision after laser therapy[21], indicating the necessity of improving the current therapy plan. This study explored the efficacy of laser photocoagulation combined with LU on RAM, to assess whether this combination can be a better choice for future clinical therapy of RAM.

In this study, we first compared the clinical efficacy between the two groups, and found a notably higher total effective rate in the Obs group than in the Con group, suggesting the remarkable effect of laser photocoagulation combined with LU on RAM. The results of this study are consistent with the research done by Tadayoni et al.[22] on the application of laser photocoagulation combined with LU in retinal branch vein occlusion, supporting our results. As we all know, during the development of RAM, the bleeding and exudation induced by RAM rupture can directly give rise to retinal hypoxia and osmotic pressure change, destroying the normal structure of retinal barrier and causing a large amount of lipid exudation and serious detachment of retina, finally resulting in irreversible damage to retinal photoreceptor.[23] Also, Early Treatment Diabetic Retinopathy Study (ETDRS) revealed the post-therapy potential side effects of laser photocoagulation therapy with decreased visual acuity, possibly due to the formation of the macular edema.[10] Therefore in this study we investigated safety of the combinational treatment. The Obs group showed a lower incidence of adverse reactions than the Con group, which also implied the higher safety and application value of laser photocoagulation combined with LU than that of laser photocoagulation alone.

In laser therapy, the commonly used low-power laser beam has favorable refractive interstitial transmittance for the normal eyes however can hardly penetrate the mixture of blood and lipid[24], so effective repair of the broken RAM with laser therapy is impossible. Moreover, increasing the power may cause photothermal burns to the retina and surrounding tissues. Therefore, multiple and repeated laser treatments are needed to repair the damaged RAM tissues step by step. Comparative results of the required numbers of laser therapy between the two groups in this study can also preliminarily verify this view.

The LUMINOUS study conducted by Mitchell et al.[25] on patients with diabetic macular edema supported that monoclonal antibody ranibizumab; showed improvements in visual acuity. Similarly in this study, LU applied in the Obs group along with laser photocoagulation strongly suppressed the activity of VEGF in retinal tissue, reduced the development of edema, vascular endothelial cells and neovascularization, and thus alleviated vascular penetration. It was conducive to the direct effect of laser on tumor, and improved the efficacy on patients. Laser therapy may aggravate the inflammatory reaction of retina tissue and give rise to the increase of arterial pressure and intraocular pressure, which is also one key reason for adverse reactions and unfavorable efficacy on patients.[26] In this study a combinational treatment showed favorable clinical efficacy in patients along with the reduction in the adverse reactions.

The application of LU can destroy the photoreceptor complex and reduce the oxygen consumption of the outer retina, which can lower the intraocular pressure, and can also inhibit the activity of inflammatory mediators participating in the process of retinopathy,[27] thus improving the efficacy on and safety to patients. This can be confirmed by our subsequent comparison of BCVA, CMT and intraocular pressure between the two groups. These results indicate that laser photocoagulation combined with LU can not only deliver higher efficacy on RAM, but also shorten the rehabilitation cycle and laser therapy times required for the patients. The follow-up results also fully confirmed that the Obs group had better long-term prognosis, which solved the key problem of RAM in current clinical treatment. The results were strongly bound up with the remarkable efficacy of laser photocoagulation combined with LU.

Finally, through the analysis of related factors, we found that dilation diameter, BCVA after therapy, CMT after therapy, intraocular pressure after therapy, and therapy methods were independent risk factors for patients' visual function. Therefore, the unfavorable prognosis of some patients after laser therapy is strongly associated with the

insignificant effect of laser therapy, which also suggests the strong necessity to implement laser photocoagulation combined with LU for patients with RAM.

However, this study still has many limitations. For instance, we have not set RAM patients treated with LU alone as a control, and all patients in this study are patients with early aneurysms, so the effect of laser photocoagulation combined with LU on middle and late stage patients is worth further exploring. Due to the lack of relevant research support, it is uncertain whether the injection time of LU affects the efficacy on RAM. In future, we need to follow up the subjects enrolled in this study for a longer time. These are the emphases and directions of our follow-up research. We will make more comprehensive and detailed experimental analysis on the application of laser photocoagulation combined with LU to get the best results for clinical reference.

CONCLUSION

Compared to single laser photocoagulation treatment, laser photocoagulation combined with LU can deliver higher clinical efficacy and safety for patients with RAM. Combined treatment can shorten the rehabilitation cycle of patients, and provide excellent guarantee for patients' long-term prognosis, favoring its use in the clinical practice to treat patients suffering from RAM. However, there is a need of further study on the clinical efficacy and safety profile of the LU alone along with a follow-up research after therapies in patients with RAM.

COMPETING INTERESTS

The authors report no conflict of interest.

AUTHOR CONTRIBUTIONS

Sha Liu and Yan Wang have made equal contributions to this work

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