Tropical Journal of Pharmaceutical Research February 2022; 21 (2): 417-423
ISSN: 1596-5996 (print); 1596-9827 (electronic)
© Pharmacotherapy Group, Faculty of Pharmacy, University of Benin, Benin City, 300001 Nigeria.

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v21i2.27

Original Research Article

Efficacy and safety of a combination of shuangdan mingmu capsules and laser therapy for diabetic retinopathy, and its effect on blood glucose indices and quality of life of patients

Rui Zhang[1], Boru Feng[2]*
[1]Department of Ophthalmology, Beijing FengTai Hospital, Teaching Hospital of Capital Medical University, Beijing 100070, [2]Department of Ophthalmology, Zhenba County Peoples Hospital, Shaanxi 723600, China

For correspondence: **Email: fk0dt3@163.com*

Sent for review: 9 September 2021 *Revised accepted: 29 January 2022*

Abstract

Purpose: *To investigate the efficacy and safety of a combination of Shuangdan Mingmu capsules and laser therapy in diabetic retinopathy (DR), as well as on blood glucose index and quality of life.*
Methods: *One hundred and twenty DR patients admitted to Zhenba County Peoples Hospital, Shaanxi were assigned equally to 2 groups: A and B. Retinal laser photocoagulation was performed for group B patients, while Shuangdan Mingmu capsules were given to group A, in addition to laser treatment. Ophthalmic parameters, blood glucose indices, ultrasonic indices, platelet parameters, quality of life, and incidence of adverse drug reactions (ADR) were determined and compared between groups A and B.*
Results: *Following treatment, group A had significantly better ophthalmic parameters, blood glucose indices and platelet parameters ($p < 0.05$); better ultrasonic indices and quality of life ($p < 0.001$), and lower ADRs ($p < 0.05$) than group B.*
Conclusion: *The combination of Shuangdan Mingmu capsules and laser therapy effectively cures ocular lesions, controls blood glucose, and lowers ADR in DR patients. Therefore, the combined therapy should be further investigated for the management of diabetic retinopathy.*

Keywords: *Shuangdan Mingmu capsules, Retina laser photocoagulation, Diabetic retinopathy*

This is an Open Access article that uses a funding model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0) and the Budapest Open Access Initiative (http://www.budapestopenaccessinitiative.org/read), which permit unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited.

Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, International Pharmaceutical Abstract, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Disorder in glucose metabolism is a fundamental feature of diabetic patients. Long-term disorder in glucose metabolism leads to chronic inflammation and disturbance in microcirculation. The disorder impairs endothelial function, increases blood viscosity, and causes platelet deposition and attachment, thereby resulting in thrombosis and microvascular lesions [1-3]. Retinopathy is a manifestation of microvascular lesions, the severity and pathogenesis of which are closely related to parameters such as blood glucose, blood lipids and platelets. Retinopathy patients may lose their vision irreversibly, leading to poor quality of life. Currently, vascular

© 2022 The authors. This work is licensed under the Creative Commons Attribution 4.0 International License

endothelial factor inhibitors and other drugs are used to treat diabetic retinopathy (DR) in clinical practice, but this treatment is minimally effective in most patients, and it leads to various adverse effects, resulting in poor prognosis. Retinal laser photocoagulation is the preferred treatment for DR patients in the proliferating phase, but it has limited clinical application because it induces changes in color sense and damages normal tissues in patients [4-7].

Traditional Chinese medicine (TCM) holds that the treatment of DR should be started with *invigorating blood circulation* and *eliminating stasis*, as well as improving microcirculation level, all of which play positive roles in nourishing the liver, thereby improving visual acuity. The glossy privet fruit, *yerbadetajo* herb and other herbs in *shuangdan Mingmu* capsule are effective in nourishing the liver, and the capsule is beneficial to the organs and tissues, while alleviating the patient's condition [8-11]. Theoretically, combined treatment using the capsule and laser therapy is expected to relieve the adverse effects, and reduce tissue damage due to the application of laser therapy alone, leading to a radical treatment effect.

Based on this, 120 DR patients admitted to *Zhenba County Peoples Hospital* from January 2019 to January 2020, were selected as the research subjects for studying the actual efficacy of combination of *Shuangdan Mingmu* capsules with laser therapy.

METHODS

General patient information

One hundred and twenty DR patients admitted to our hospital within the specified period served as research subjects. They were equally assigned to 2 groups which were comparable with respect to basic biodata (Table 1). Approval for this investigation was received from the ethical committee of *Zhenba County Peoples Hospital (approval no. 20181199).* The study also followed international guidelines for human studies. Signed informed consent was obtained from each patient or a family representative.

Inclusion criteria

Patients who were diagnosed with type 2 diabetes and with DR after ophthalmic examination and optical coherence tomography [12]; patients with no history of ocular surgery, and no other ocular diseases, and patients who could be treated with retinal laser photocoagulation [13], were included in this study.

Exclusion criteria

Mentally-challenged patients and those with difficulties in communication; patients who had other serious illnesses including anterior disease of eye [14], and patients with familial medical history of ocular hypertension [15], were excluded.

Table 1: Comparison of general information on patients

Group	Group A (n = 60)	Group B (n = 60)	χ^2/t	*P*-value
Gender			0.035	0.853
Male	35	36		
Female	25	24		
Age (years)				
Range	55-74	54-74		
Mean	62.15±5.65	62.98±5.15	0.841	0.402
Hypertension	15	16	0.044	0.835
Coronary heart disease	12	13	0.051	0.822
Lung disease	10	8	0.261	0.609
Disease stage				
I	29	30	0.033	0.855
II	15	16	0.044	0.835
III	16	14	0.178	0.673
Duration of disease (years)	3.65±0.65	3.62±0.58	0.267	0.790
Educational qualification			0.034	0.855
Senior high school and lower	28	27		
College and higher	32	33		
Monthly income (Yuan)			0.044	0.835
≤ 3000	15	16		
> 3000	45	44		

Treatments

Retinal laser photocoagulation was performed in group B, while group A received *Shuangdan Mingmu* capsules, in addition to retinal laser photocoagulation, with specific steps as follows: all patients underwent visual acuity examination in order to measure their unaided visual acuity and corrected visual acuity. Then, intraocular pressure was measured using a non-contact tonometer (Tianjin Suowei Electronic Technology Co. Ltd.; Tianjin Medical Device license no. 20202160142). Thereafter, the patients were examined with a conventional slit lamp (Suzhou 66 Vision Tech Co. Ltd.; Suzhou Medical Device license no. 20182220269) and retinal photography (Fuzhou Resta Photoelectric Technology Co. Ltd; Fujian Medical Products Administration Certified no. 20112220045). Before treatment, compound tropicamide eye drops (Univision Pharmaceutical Co. Ltd.; NMPA approval no. H20066782) was given every 10 min. After three mydriasis, oxybuprocaine (Shenyang Luzhou Pharmaceutical LLC; NMPA approval no. H21023201) was given every 10 min twice a day.

Retinal laser photocoagulation therapy was implemented as follows: using ofloxacin ophthalmic ointment (Shenyang Sinqi Ophthalmic Medications Holdings Co. Ltd.; NMPA approval no. H10940177) as the coupling agent, the pan-retinal ophthalmic therapeutic apparatus (Meridian AG; NMPA (I) 20153161981) was used for photocoagulation every two weeks, for 1 month. For *shuangdan mingmu* capsule therapy, the patients took 60 g of *shuangdan mingmu* capsule (Beijing Qihuang Pharmaceutical Manufacturing Co. Ltd.; NMPA approval no. Z20080062) orally, thrice daily for 12 weeks.

Evaluation of treatment indices

Ophthalmic parameters

Comparison was done on the best corrected visual acuity, central macular thickness and leakage area between A and B before treatment, 4 weeks post-treatment, and 12 weeks post-treatment.

Blood glucose indexes

Comparison of levels of fasting blood glucose, standard deviation in blood glucose, and absolute deviation in blood glucose was done between groups A and B before treatment, 4 weeks post-treatment, and 12 weeks post-treatment.

Ultrasonic indexes

The end diastolic velocity (EDV), peak systolic velocity (PSV) and resistant index (RI) of central artery of retina and ophthalmic artery of patients were compared between the two groups 3 months after treatment.

Platelet parameters

The CD62p, CD63 and mean platelet volume of patients were compared between the two groups before treatment, 4 weeks post-treatment and 12 weeks post-treatment.

Quality of life

Three months after treatment, quality of life (QOL) was measured using GQOLI-74 scale which covered four dimensions of social function, physical function, psychological function and material life (0 - 100 points). Higher scores indicated higher QOL [16].

Incidence of adverse reactions (ARR)

The adverse reactions included gastrointestinal reaction, light-headedness, fervescence, and elevated intraocular pressure. The numbers of patients with adverse reactions were recorded.

Statistical analysis

The SPSS version 20.0 software was used for analysis of results, while GraphPad Prism 7 was employed for graphics. Counted and measured data were compared between groups A and B using chi square (χ^2) test and *t*-test, respectively. Values of $p < 0.05$ were taken as indicative of statistical significance.

RESULTS

Ophthalmic indices

Post-treatment ophthalmic parameters were markedly better in A than in B.

Blood glucose indices

After treatment, the blood glucose indexes were markedly better in group A than in group B.

Ultrasonic indices

After treatment, the ultrasonic indexes were significantly better in group A than in group B.

Table 2: Ophthalmic indices for groups A and B (mean ± SD)

Ophthalmic index	Group A	Group B	t	*P*-value
Best corrected visual acuity				
Before treatment	0.04±0.01	0.26±0.09	0.000	1.000
4 weeks after therapy	0.04±0.02	0.45±0.14	8.843	<0.001
12 weeks after therapy	0.24±0.05	0.41±0.06	16.860	<0.001
Central macular thickness (μm)				
Before treatment	458.65±20.11	460.98±22.68	0.595	0.553
4 weeks after therapy	350.98±23.68	402.98±24.51	11.819	<0.001
12 weeks after therapy	284.15±35.12	350.64±35.11	10.371	<0.001
Leakage area (mm^2)				
Before treatment	2.10±1.21	2.04±1.20	0.273	0.786
1 m post-treatment	1.68±0.54	1.92±0.59	2.324	0.022
3 m post-treatment	1.38±0.22	1.54±0.32	3.192	0.002

Table 3: Values of blood glucose indices in the 2 groups (mean ± SD)

Blood glucose index	Group A	Group B	*t*	*P*
Fasting blood glucose (mmol/L)				
Before treatment	9.10±1.21	9.05±1.22	0.225	0.822
4 weeks after therapy	7.98±1.00	8.55±1.20	2.827	0.006
12 weeks after therapy	7.00±1.01	7.84±1.04	4.488	<0.001
Standard deviation of blood glucose (mmol/L)				
Before treatment	2.74±0.35	2.75±0.32	0.163	0.871
4 weeks after therapy	1.95±0.24	2.55±0.26	13.135	<0.001
12 weeks after therapy	1.65±0.21	1.94±0.20	7.746	<0.001
Absolute deviation of blood glucose (mmol/L)				
Before treatment	5.98±1.26	5.87±1.11	0.507	0.613
4 weeks after therapy	3.41±1.24	4.56±0.98	5.636	<0.001
12 weeks after therapy	1.98±0.54	2.56±0.58	5.669	<0.001

Table 4: Values of post-treatment ultrasonic indices (mean ± SD)

Ultrasonic index	Group A	Group B	*t*	*P*-value
Central artery of retina				
EDV (cm/s)	3.05±0.75	2.36±0.58	5.637	< 0.001
PSV (cm/s)	9.45±1.10	8.84±0.98	3.207	0.002
RI	1.30±0.21	1.55±0.23	6.218	< 0.001
Ophthalmic artery				
EDV (cm/s)	9.15±1.03	7.54±1.00	8.687	< 0.001
PSV (cm/s)	35.41±5.68	28.12±5.45	7.173	< 0.001
RI	0.74±0.05	0.84±0.08	8.211	< 0.001

Table 5: Comparison of platelet parameters (mean ± SD)

Platelet parameter	Group A	Group B	*t*	*P*-value
CD62p (%)				
Before treatment	9.56±1.21	9.44±1.20	0.545	0.587
4 weeks after therapy	7.98±1.01	8.44±1.24	2.228	0.028
12 weeks after therapy	6.54±1.20	8.10±1.21	7.091	< 0.001
CD63 (%)				
Before treatment	10.54±2.15	10.55±2.41	0.024	0.981
4 weeks after therapy	8.98±1.65	9.45±1.54	1.613	0.109
12 weeks after therapy	7.51±1.62	8.45±1.57	3.228	0.002
Mean platelet volume (Vf/L)				
Before treatment	9.54±1.21	9.65±1.25	0.490	0.625
4 weeks after therapy	8.21±1.20	8.95±1.26	3.294	0.001
12 weeks after therapy	7.98±1.23	8.55±1.58	2.205	0.029

Table 6: Comparison of quality of life after treatment (mean±SD, points)

Parameter	Group A	Group B	*t*	*P*-value
Psychological function	84.21±5.21	74.65±5.98	9.337	< 0.001
Physical function	82.65±5.22	72.51±5.32	10.538	< 0.001
Social function	87.65±3.51	79.98±5.41	9.213	< 0.001
Material life	88.65±4.25	80.15±4.32	10.865	< 0.001

Table 7: Comparison of ADR between the two groups

Reaction	Group A	Group B	X^2	*P*-value
Gastrointestinal reaction	1	3	1.035	0.309
Light-headedness	2	3	0.209	0.648
Fervescence	2	2	0.000	1.000
Elevated intraocular pressure	2	5	1.365	0.243
Total incidence	4 (6.7)	13 (21.7)	5.551	0.018

Platelet parameters

After treatment, platelet parameters were better in group A than in group B ($p < 0.05$).

Quality of life (QOL)

Post-treatment QOL was markedly better in group A patients than in group B patients, as shown in Table 6.

Adverse drug reactions (ADR)

The ADR of group A was significantly lower than that of group B ($p < 0.05$) as shown in Table 7.

DISCUSSION

Diabetic retinopathy (DR) is a manifestation of ocular microangiopathy which is caused by long-standing high blood glucose and non-enzymatic glycosylation triggered by disorder in glucose metabolism. These result in elevated free radical contents, thereby impairing endothelial function. Under such microcirculatory abnormality, neovascularization is accelerated due to the hypoxic and ischemic state, leading to retinopathy.

Clinical practice has shown that blindness easily occurs in DR patients, and the average survival time after the patients become blind is only 6 years. This indicates that DR, one of the diabetic complications associated with great harm, not only reduces the QOL of diabetic patients, but also seriously affects prognosis. Therefore, early intervention measures must be taken to safeguard the lives of DR patients. At present, retinal laser photocoagulation therapy is mostly used for treating retinal hypoxia and ischemia, guiding blood flow to the macular region, and slowing down visual impairment. However, the therapy may affect normal tissues in patients and change their sense of color after surgery. These adverse effects limit the clinical application of retinal laser photocoagulation therapy. Therefore, the future research direction on DR should be focused on obtaining a safer and more efficient therapeutic effect without causing any harm to the body tissues.

The long-term efficacy of TCM is more desirable than that of western medicine because TCM treatment is beneficial to several organs and tissues, and it treats both manifestation and root cause of disease. The use of adjuvant TCM treatment and laser therapy not only enhances comprehensive efficacy, but also reduces the damage in normal tissues. The *shuangdan mingmu* capsule used in this study contained glossy privet fruit and *yerbadetajo* herb. Glossy privet fruit works well as an anti-inflammatory agent and inhibitor of adrenaline- and glucose-induced hyperglycemia, due to its high content of oleanolic acid [17]. Moreover, it has been reported that glossy privet fruit juice exerted anti-platelet aggregation and blood lipid-lowering effects in mice [17].

Patients in group A had markedly better platelet parameters and blood glucose indexes than those in group B, suggesting that *shuangdan mingmu* capsules lowered platelet deposition and likelihood of thrombosis, and improved microcirculation. In addition, *yerbadetajo* herb contains several flavonoids that are often used for treating cardio-cerebrovascular ailments; it exerts anti-inflammatory and anti-free radical effects, lowers plasma lipid levels, and enhances vascular flow. Thus, group A had better ultrasonic indexes (central artery of retina and ophthalmic artery) after treatment, than group B.

The central artery of retina is essential for the maintenance of vision, and it is the source of retinal nutrients. The ophthalmic artery supplies all layers of the retina. The enhanced blood supply due to *yerbadetajo* herb enabled better

perfusion and increased nutrient supply to the retina. Thus, after treatment, ophthalmic parameters were markedly better in group A than in group B, as a result of the use of combination of glossy privet fruit, *yerbadetajo* herb and laser therapy.

In this study, the quality of life of group A after treatment was clearly better than that of group B. This is consistent with the findings of Dhoot *et al*. [18]. In that research, DR patients were given a combination of glossy privet fruit juice and laser therapy, while the control group received laser therapy alone. The results revealed that the experimental group had significantly higher GQOLI-74 scores than the control patients [17]. This was due to fact that the experimental group had better visual recovery, and their tissues were well-protected, since the toxic side effect of TCM materials was slight. Therefore, combined therapy not only prevented the adverse reactions induced by crude Chinese drugs, but also reduced the damage to normal tissues caused by laser therapy, resulting in a lower ARR and better quality of life.

CONCLUSION

Combined treatment with *shuangdan mingmu* capsules and laser therapy cures ocular lesions in DR patients, controlls blood glucose indices, and lowers ADRs. Therefore, the combination therapy needs to be further studies for use in clinical practice.

DECLARATIONS

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. RZ conceived and designed the study, and drafted the manuscript. BF collected, analyzed and interpreted the experimental data. RZ revised the manuscript for important intellectual content. Both authors read and approved the final manuscript.

Open Access

This is an Open Access article that uses a funding model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0) and the Budapest Open Access Initiative (http://www.budapestopenaccessinitiative.org/read), which permit unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited.

REFERENCES

1. *Dahl-Jørgensen K, Brinchmann-Hansen O, Hanssen KF, Ganes T, Kierulf P, Smeland E, Sandvik L, Aagenaes O. Effect of near normoglycaemia for two years on progression of early diabetic retinopathy, nephropathy, and neuropathy: The Oslo study. Br Med J (Clin Res Ed) 1986; 293: 1195-1199.*
2. *Ruamviboonsuk P, Tiensuwan M, Kunawut C, Masayaanon P. Repeatability of an automated Landolt C test, compared with the early treatment of diabetic retinopathy study (ETDRS) chart testing. Am J Ophthalmol 2003; 136: 662-669.*
3. *Voets M, Møllersen K, Bongo LA. Replication study: Development and validation of deep learning algorithm for detection of diabetic retinopathy in retinal fundus photographs. PLoS One 2019; 14: e0217541.*
4. *Carbonell M, Castelblanco E, Valldeperas X, Betriu À, Traveset A, Granado-Casas M, Hernández M, Vázquez F, Martín M, Rubinat E, et al. Diabetic retinopathy is associated with the presence and burden of subclinical carotid atherosclerosis in type 1 diabetes. Cardiovasc Diabetol 2018; 17: 66.*
5. *McDowell RE, Barabas P, Augustine J, Chevallier O, McCarron P, Chen M, McGeown JG, Curtis TM. Müller glial dysfunction during diabetic retinopathy in rats is reduced by the acrolein-scavenging drug, 2-hydrazino-4,6-dimethylpyrimidine. Diabetologia 2018; 61: 2654-2667.*
6. *Ren L, Zhang Z, Li D, Deng C, Tao H. Clinical efficacy of semiconductor laser-assisted minocycline in moderate-to-severe chronic periodontitis patients with type 2 diabetes mellitus. Trop J Pharm Res 2018; 17: 1165-1170*
7. *Lee MY, Hsiao PJ, Huang JC, Hsu WH, Chen SC, Chang JM, Shin SJ. Abnormally Low or High Ankle-Brachial Index Is Associated With the Development of Diabetic Retinopathy in Type 2 Diabetes Mellitus. Sci Rep 2018; 8: 441.*
8. *Keel S, Lee PY, Scheetz J, Li Z, Kotowicz MA, MacIsaac RJ, He M. Feasibility and patient acceptability of a novel artificial intelligence-based screening model for diabetic retinopathy at endocrinology outpatient services: a pilot study. Sci Rep 2018; 8: 4330.*
9. *Tsai T, Kuehn S, Tsiampalis N, Vu MK, Kakkassery V, Stute G, Dick HB, Joachim SC. Anti-inflammatory cytokine and angiogenic factors levels in vitreous samples of diabetic retinopathy patients. PLoS One 2018; 13: e0194603.*

10. Herat LY, Matthews VB, Rakoczy PE, Carnagarin R, Schlaich M. Focusing on Sodium Glucose Cotransporter-2 and the Sympathetic Nervous System: Potential Impact in Diabetic Retinopathy. Int J Endocrinol 2018; 2018: 9254126.
11. Lu Y, Simonett JM, Wang J, Zhang M, Hwang T, Hagag AM, Huang D, Li D, Jia Y. Evaluation of Automatically Quantified Foveal Avascular Zone Metrics for Diagnosis of Diabetic Retinopathy Using Optical Coherence Tomography Angiography. Invest Ophthalmol Vis Sci 2018; 59: 2212-2221.
12. Huang C, Fisher KP, Hammer SS, Navitskaya S, Blanchard GJ, Busik JV. Plasma Exosomes Contribute to Microvascular Damage in Diabetic Retinopathy by Activating the Classical Complement Pathway. Diabetes 2018; 67: 1639-1649.
13. Lingam S, Rani PK, Sheeladevi S, Kotapati V, Das T. Knowledge, attitude and practices on diabetes, hypertension and diabetic retinopathy and the factors that motivate screening for diabetes and diabetic retinopathy in a pyramidal model of eye health care. Rural Remote Health 2018; 18: 4304.
14. Vetrini D, Kiire CA, Burgess PI, Harding SP, Kayange PC, Kalua K, Msukwa G, Beare NAV, Madan J. Incremental cost-effectiveness of screening and laser treatment for diabetic retinopathy and macular edema in Malawi. PLoS One 2018; 13: e0190742.
15. Mahaling B, Srinivasarao DA, Raghu G, Kasam RK, Bhanuprakash Reddy G, Katti DS. A non-invasive nanoparticle mediated delivery of triamcinolone acetonide ameliorates diabetic retinopathy in rats. Nanoscale 2018; 10: 16485-16498.
16. Kawasaki R, Kitano S, Sato Y, Yamashita H, Nishimura R, Tajima N, Japan Diabetes Complication and its Prevention prospective (JDCP) study Diabetic Retinopathy working group. Factors associated with non-proliferative diabetic retinopathy in patients with type 1 and type 2 diabetes: the Japan Diabetes Complication and its Prevention prospective study (JDCP study 4). Diabetol Int 2018; 10: 3-11.
17. Lee YH. Socioeconomic differences among community-dwelling diabetic adults screened for diabetic retinopathy and nephropathy: The 2015 Korean Community Health Survey. PLoS One 2018; 13: e0191496.
18. Dhoot DS, Baker K, Saroj N, Vitti R, Berliner AJ, Metzig C, Thompson D, Singh RP. Baseline Factors Affecting Changes in Diabetic Retinopathy Severity Scale Score After Intravitreal Aflibercept or Laser for Diabetic Macular Edema: Post Hoc Analyses from VISTA and VIVID. Ophthalmology 2018; 125: 51-56.