Tropical Journal of Pharmaceutical Research March 2024; 23 (3): 571-577
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v23i3.11

Original Research Article

Calcium dobesilate combined with candesartan in the treatment of proliferative diabetic retinopathy and its effect on TGF-b1, VEGF and IL-19 levels in the vitreous humor

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Sent for review: 23 September 2023 *Revised accepted: 25 February 2024*

Abstract

Purpose: *To investigate the efficacy of a combination therapy involving calcium dobesilate and candesartan in the treatment of proliferative diabetic retinopathy and its impact on the transforming growth factor b1 (TGF-b1), vascular endothelial growth factor (VEGF) and interleukin-19 (IL-19) levels in the vitreous humor.*
Methods: *Between January 2020 and May 2023, 112 patients with proliferative diabetic retinopathy from Handan City Eye Hospital, China were enrolled in this study. They were divided into two groups: study group (n = 56) - orally administered 500 mg of calcium dobesilate combined with 50 mg of candesartan daily - and control group (n = 56), received calcium dobesilate only. Patients began treatment with calcium dobesilate and candesartan as soon as diabetic retinopathy was diagnosed. Treatment efficacy, changes in hemorrhage area, macular thickness and best-corrected visual acuity were assessed before and after treatment (for a duration of 60 days).*
Results: *Study group had significantly higher ($p < 0.05$) treatment efficacy compared to control group, achieving a total effective rate of 92.86 %. It also exhibited reduced hemorrhage area and macular thickness, which were significantly lower ($p < 0.05$) than those in control group. Best-corrected visual acuity was significantly higher in the study group ($p < 0.05$) followed by improved peak systolic velocity and end-diastolic velocity after treatment ($p < 0.05$). Additionally, TGF-b1, VEGF and IL-19 levels in the vitreous humor were significantly lower in study group compared to control group ($p < 0.05$).*
Conclusion: *The combination of calcium dobesilate and candesartan demonstrates significant therapeutic efficacy in treating proliferative diabetic retinopathy while reducing the TGF-b1, VEGF and IL-19 levels in the vitreous humor. Large-scale studies are needed to validate these findings and delve into treatment mechanisms and long-term effects.*

Keywords: *Calcium dobesilate, Candesartan, Proliferative diabetic retinopathy, Efficacy, Transforming growth factor b1, Vascular endothelial growth factor, Interleukin-19*

Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, Web of Science, 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

Proliferative Diabetic Retinopathy (PDR) is a severe complication of late-stage diabetes, characterized by the formation of new blood vessels and secondary hemorrhage [1]. The underlying pathological mechanisms of this disease are associated with the overexpression of various growth factors and cytokines, among which Transforming Growth Factor β1 (TGF-β1),

Vascular Endothelial Growth Factor (VEGF) and Interleukin-19 (IL-19) play core roles [2]. Specifically, VEGF is pivotal in the formation of new blood vessels, promoting their growth but these newly formed vessels are fragile and prone to bleeding [3]. Transforming Growth Factor β1 (TGF-β1) is involved in the fibrotic process of diabetic retinas while IL-19 is associated with ocular inflammation and immune responses [4]. Therefore, reducing the levels of these cytokines is a key strategy in preventing and treating PDR.

Calcium dobesilate is a drug commonly used to treat some eye diseases, especially retinal diseases. Its mechanism of action includes improving microcirculation, reducing inflammatory responses and combating oxidative stress. This drug helps improve the blood supply to the retina and thus has a positive impact on some retina-related diseases [5]. On the other hand, Candesartan is a recombinant fusion protein designed to efficiently bind with VEGF to inhibit its activity [6]. Therefore, combining calcium dobesilate with Candesartan is expected to achieve better therapeutic results, especially in the treatment of eye diseases such as proliferative diabetic retinopathy (PDR).

This combination treatment helps protect retinal health by improving retinal blood supply, reducing inflammation, combating oxidative stress and inhibiting abnormal angiogenesis. However, study on the combination of calcium dobesilate and candesartan for PDR treatment is still limited and further empirical studies are needed to prove their effectiveness and impact on cytokine levels.

This study therefore investigates the efficacy of calcium dobesilate combined with candesartan in treating PDR and its influence on the TGF-β1, VEGF and IL-19 levels. The aim is to provide valuable insights for the development of more scientific and effective treatment strategies.

METHODS

General patient information

A total of 112 patients with PDR were enrolled for this study at Handan City Eye Hospital (The Third Hospital of Handan), Handan, China from January 2020 to May 2023. Patients were equally divided into study and control groups, using an envelope method [6]. This study received approval from the Hospital's Ethics Committee (approval no. 2020001) and was performed by following the guidelines in the Declaration of Helsinki [7].

Inclusion criteria

Patients diagnosed with the disease following the practice guidelines [8]; patients with unilateral retinal lesions, retinal lesions confirmed by fundus fluorescein angiography as stage I to III, stable blood glucose control with fasting blood glucose ≤ 7 mmol/L and postprandial blood glucose ≤ 12 mmol/L; no history of ocular surgery and provided informed consent either from the patients or their families were included in the study.

Exclusion criteria

Patients with the presence of concomitant eye diseases such as retinal vasculitis or central retinal vein occlusion or the presence of other serious illnesses, such as malignancies, hypertension, cardiovascular diseases, or autoimmune disorders were excluded.

Treatments

Control group received calcium dobesilate capsules (Guizhou Tianan Pharmaceutical Co. Ltd, Guiyang, China; National Medical Products Administration approval no. H20010481) administered orally at a frequency of 1 capsule, three times a day, for a treatment period of 90 days [8]. On the other hand, study group received valsartan (6 mg once daily) in addition to control group treatment. In the three days leading up to the surgery, patients were given levofloxacin eye drops, with 1 - 2 drops administered each time, along with necessary related examinations. On the day of surgery, patients were placed in a sterile laminar flow operating room and positioned in a supine position. Anesthetic treatment was administered to the surface of the eye using oxybuprocaine hydrochloride (Japan Santen Pharmaceutical Co. Ltd; National Medical Products Administration approval no. HJ20215002), followed by cleaning the conjunctival sac with polyvinyl alcohol iodine (Guangdong Kexin Pharmaceutical Co. Ltd, Guangzhou, China; National Medical Products Administration approval no. H44023383). After routine disinfection and draping, an eyelid opener was used to expose the eyeball.

Subsequently, a tunnel technique was employed and a vertical puncture into the vitreous cavity was made 3.5 mm posterior to the corneal edge. Injection of candesartan eye injection solution (Germany Vetter Pharma-Fertigung GmbH & Co. KG; National Medical Products Administration approval no. SJ20235001) into the vitreous cavity was then gradually carried out at 0.05 mL per injection, once a month, for a total of three

injections. The decision to continue the injections depended on the progress of the patient's condition. After completing the injection, the needle was quickly removed and the puncture site was gently pressed with a sterile cotton swab for 30 seconds. Some aqueous humor was slightly released from the edge of the transparent cornea to ensure intraocular pressure stability.

Evaluation of parameters/indices

Treatment efficacy/effectiveness

After three months of treatment, the treatment effect was assessed following the previously reported method [9]. *Marked improvement* (Significant): Symptoms such as retinal bleeding and hemorrhage disappeared, the visual field expanded by 10° - 15° and visual acuity improved by ≥ 3 lines; *Improvement* (Good): Partial disappearance of symptoms such as retinal bleeding and hemorrhage, an expansion of the visual field by 5° - 10° and an improvement in visual acuity by 2 lines; *No improvement* (Ineffective): No change or worsening of symptoms such as retinal bleeding and hemorrhage, with no improvement in the visual field or visual acuity as per the above criteria. The overall effective rate was calculated as the sum of the marked improvement and improvement rates.

Optical coherence tomography

Optical coherence tomography (OCT) was used to determine macular thickness [9]. A 3D OCT-2000 optical coherence tomography scanner (Beijing, China) was employed for this purpose. The area of hemorrhage spots was quantified using a projection visual field examination device (Chongqing, China).

Visual acuity testing

Visual acuity was tested using the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity chart at a distance of 2 meters. The best-corrected visual acuity was determined by following a standard refraction procedure to determine the number of letters corresponding to the best-corrected visual acuity.

Peak systolic velocity

Peak systolic velocity (PSV) and end-diastolic velocity (EDV) were measured and calculated for both patient groups using a Philips HD7 color Doppler ultrasound device.

During the surgical procedure, vitreous humor samples were obtained from the patient's eyes.

Determination of the levels of cytokines

Enzyme-linked immunosorbent assays (ELISA) was employed to determine the levels of TGF-β1, VEGF, and IL-19.

Statistical analysis

Statistical analysis was done using Statistic Package for Social Sciences (SPSS 22.0) software (IBM, Armonk, NY, USA). Continuous data, including age, duration of diabetes, fasting blood glucose and descriptive statistics, were presented as mean ± standard deviation (SD). Differences between groups were analyzed using the *t*-test. Categorical data, such as gender, and stage of retinal lesions, were presented as percentages. Differences between groups were analyzed using the Chi-square test or rank-sum test, as appropriate. Differences between groups were considered statistically significant when the *p*-value was less than 0.05.

RESULTS

Patients' information

The baseline characteristics of both groups are summarized in Table 1.

Treatment efficacy

The treatment efficacy in study group was significantly better than that in control group ($p < 0.05$). The overall effective rate in study group was 92.86 % compared to 85.71 % in control group, as shown in Table 2.

Hemorrhage area, macular thickness and best-corrected visual acuity

There were no statistically significant differences in hemorrhage area, macular thickness and best-corrected visual acuity between the study and control groups before treatment ($p > 0.05$). However, after treatment, both the study and control groups showed improvements in hemorrhage area, macular thickness and best-corrected visual acuity ($p < 0.05$). Notably, study group exhibited significantly lower hemorrhage area and macular thickness compared to control group ($p < 0.05$), while the best-corrected visual acuity was significantly higher in study group compared to control group ($p < 0.05$). Detailed data are shown in Table 3.

Table 1: Comparison of basic information between the groups (n=56)

Group	Sex		Age (years)	Diabetes duration (years)	Retinopathy stage			Fasting blood glucose (mmol/L)	HbA1c (%)
	Male	Female			I	II	III		
Study	23 (41.07)	33 (58.93)	50.46±38.11	11.41±2.63	19 (33.93)	24 (42.86)	13 (23.21)	6.44±1.01	6.82±1.05
Control	20 (35.71)	36 (64.29)	51.37±7.05	11.50±2.13	17 (30.36)	27 (48.21)	12 (21.43)	6.50±1.03	6.78±1.04
t/c^2	0.340		-0.099	-0.199	0.328			-0.311	0.203
P-value	0.560		0.921	0.843	0.849			0.756	0.840

Table 2: Comparison of treatment efficacy between the two groups

Group	Significant	Good	Ineffective	Overall effective rate (%)	Z	*P*-value
Study	44 (78.57)	8 (14.29)	4 (7.14)	92.86	-2.377	0.017
Control	32 (57.14)	16 (28.57)	8 (14.29)	85.71		

Table 3: Comparison of hemorrhage area, macular thickness and best-corrected visual acuity before and after treatment

Group	Hemorrhage area (mm^2)		Macular thickness (mm)		Best-corrected visual acuity	
	Before treatment	*After treatment*	*Before treatment*	*After treatment*	*Before treatment*	*After treatment*
Study	2.87±0.45	1.12±0.40*,a	340.54±12.24	297.84±11.50*,a	0.20±0.08	0.39±0.09*,a
Control	2.85±0.52	1.72±0.38*	342.27±13.80	318.87±11.76*	0.21±0.09	0.30±0.08*
T	0.218	-8.138	-0.702	-9.568	-0.621	5.593
P-value	0.828	0.000	0.484	0.000	0.536	0.000

Note: *$P < 0.05$ vs. before treatment; $^a p < 0.05$ vs. control group after treatment

Table 4: Comparison of central retinal arterial blood flow before and after treatment

Group	Peak systolic velocity (cm/s)		End-diastolic velocity (cm/s)	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Study	5.22±0.97	9.14±0.91*,a	2.21±0.82	4.53±0.91*,a
Control	5.28±0.92	8.30±0.88*	2.18±0.79	3.61±0.96*
T	-0.336	4.966	0.197	5.205
P-value	0.738	0.000	0.844	0.000

Note: *$P < 0.05$ vs. before treatment; $^a p < 0.05$ vs. control group after treatment

Table 5: Comparison of TGF-β1, VEGF, and IL-19 levels in vitreous humor before and after treatment.

Group	TGF-β1 (ng/mL)		VEGF (mg/L)		IL-19 (pg/mL)	
	Pre-treatment	*Post-treatment*	*Pre-treatment*	*Post-treatment*	*Pre-treatment*	*Post-treatment*
Study	0.87±0.19	0.52±0.11*,a	178.81±20.41	80.45±18.77*,a	35.54±9.98	15.54±4.69*,a
Control	0.89±0.20	0.67±0.17*	180.15±22.16	125.50±20.15*	36.70±9.12	21.17±5.12*
T	-0.543	-5.544	-0.333	-12.242	-0.642	-6.068
P-value	0.589	0.000	0.740	0.000	0.522	0.000

Note: *$P < 0.05$ vs. before treatment; $^a p < 0.05$ vs. control group after treatment

Central retinal arterial blood flow

There were no significant differences in peak systolic velocity (PSV) and end-diastolic velocity (EDV) between the study and control groups before treatment ($p > 0.05$). However, after treatment, both the study and control groups showed improvements in PSV and EDV ($p < 0.05$). Notably, study group exhibited significantly higher PSV and EDV after treatment compared to control group ($p < 0.05$; Table 4).

TGF-β1, VEGF and IL-19 levels in vitreous humor

There were no statistically significant differences in TGF-β1, VEGF and IL-19 levels in the vitreous humor between the study and control groups before treatment ($p > 0.05$). However, after treatment, both the study and control groups showed decreases in TGF-β1, VEGF and IL-19 levels in the vitreous humor ($p < 0.05$). Study group exhibited significantly lower levels of TGF-β1, VEGF and IL-19 in the vitreous humor after

treatment compared to control group ($p < 0.05$). Detailed data are shown in Table 5.

DISCUSSION

Diabetic retinopathy is one of the most common ocular complications in diabetic patients, characterized by pathological features such as retinal microvascular changes, hemorrhages, edema and neovascularization, which can ultimately lead to blindness [9]. Proliferative Diabetic Retinopathy (PDR) is a rapidly progressing subtype and some studies have implicated factors like VEGF, TGF-β1 and IL-19 in the pathology of PDR [10].

Calcium dobesilate, a vascular-regulating medication, has been proven to significantly reduce capillary permeability. Additionally, it inhibits sorbitol generation, helping alleviate local microcirculation issues and reducing the risk of retinal exudation and hemorrhage caused by diabetes [11]. However, despite its ability in temporarily relieving some symptoms of diabetic retinopathy, its effectiveness in halting long-term disease progression remains limited. Consequently, there is room for improvement in its efficacy. In recent years, candesartan, a novel recombinant fusion protein, has demonstrated effectiveness not only in reducing retinal vascular leakage and lowering the risk of macular edema but also in promoting the regression of abnormal retinal neovascularization. This can reduce the likelihood of hemorrhaging and fibrosis, potentially making it a new strategy for the comprehensive treatment of PDR [12].

The results of this study indicate that the treatment efficacy in study group was significantly better than in control group ($p < 0.05$). The overall treatment effective rate in study group reached as high as 92.86 %, suggesting that the combination therapy of calcium dobesilate and candesartan demonstrates a significant advantage in improving PDR. This advantage is particularly evident in terms of hemorrhage area, macular thickness and best-corrected visual acuity. Specifically, the results of this study show that after treatment, study group exhibited significantly smaller hemorrhage areas and thinner macular thickness compared to control group, and their best-corrected visual acuity was significantly higher ($p < 0.05$). This indicates that treatment received by study group contributes in reducing the size of the hemorrhage areas and macular thickness, while improving the visual acuity of patients. The rationale behind this improvement lies in the characteristics of candesartan. Candesartan is a fusion protein that binds to and captures VEGF, preventing VEGF from binding to its receptors. This blocks VEGF-mediated signal transduction and inhibits the abnormal growth of neovascularization [13]. Additionally, candesartan contains the Fc segment of human immunoglobulin, which primarily enhances protein stability and extends its half-life in the body. This means that the medication can remain in the body for a longer duration, exerting its therapeutic effect over an extended period, ultimately preserving or even improving patients' vision [14].

Proliferative Diabetic Retinopathy (PDR) is a retinal microcirculation disorder, with abnormal blood flow in the central retinal artery being one of its typical features. The results of this study show that both the study and control groups exhibited significant improvements in peak systolic velocity (PSV) and end-diastolic velocity (EDV) after treatment. However, study group outperformed control group significantly in both of these indicators ($p < 0.05$). This suggests that the combined therapy of calcium dobesilate capsules and intravitreal candesartan injection enhances the hemodynamics of the central retinal artery, thus improving retinal microcirculation and effectively improving the patients' condition [15].

Vascular Endothelial Growth Factor (VEGF) is responsible for stimulating the formation of new blood vessels. In diabetic retinopathy, excessive VEGF can lead to the growth of abnormal new blood vessels, which are often fragile and prone to bleeding or leakage, resulting in vision impairment [16]. Interleukin (IL)-19 is a cytokine that can directly act on vascular cells, influencing their function or behavior, such as promoting blood vessel formation or enhancing their integrity. Additionally, IL-19 can stimulate macrophages to secrete vascular endothelial growth factor-A (VEGF-A). Study by Li and colleagues has shown that IL-19 plays a crucial role in diabetes-induced vascular changes [17]. Furthermore, in diabetic patients, prolonged high blood sugar levels lead to the overproduction of TGF-β1 by retinal endothelial cells and macrophages. This abnormally increased TGF-β1 not only promotes blood vessel formation and cell proliferation but also enhances the migration of retinal pigment cells, fibroblasts and glial cells into the vitreous and subretinal space, further exacerbating PDR [18].

From the results of this study, both the study and control groups showed a reduction in the levels of TGF-β1, VEGF and IL-19 in the vitreous humor after treatment. However, study group exhibited a significantly greater reduction

compared to control group ($p < 0.05$). This study emphasizes the importance of the combined therapy of calcium dobesilate and candesartan in patients with diabetic retinopathy. By lowering the levels of TGF-β1, VEGF and IL-19, this combined treatment better reduces abnormal neovascularization and other adverse effects associated with PDR, thereby improving retinal health and patient vision. The effectiveness of candesartan in achieving this outcome is attributed to its specific binding to various subtypes of VEGF-A and VEGF-B, thus depriving VEGF of its biological activity [19]. Additionally, it inhibits TGF-β1, which helps to suppress the formation and expansion of retinal neovascularization, preventing secondary vascular effects, reducing retinal edema and fluid leakage, effectively stabilizing the condition. As for the mechanism by which candesartan reduces IL-19 levels, it remains unclear at present. However, a similar conclusion was reached in a study by Liu Yuanbin and colleagues [20]. They found that intravitreal injection of candesartan significantly reduced the levels of IL-19 in the vitreous humor of patients with proliferative diabetic retinopathy.

Limitations of this study

Although this study achieved some important findings, some limitations need to be considered. First, the sample size was relatively small, which may affect the broad applicability of the results. Due to the limited sample size, there is need to interpret the results with caution and be wary of overgeneralization. Additionally, this study was conducted at a single medical center, which may result in regional and population-specific factors affecting the results. To increase the external validity of the study results, multicenter study designs could be considered in the future. The time span of the study was relatively short and long-term follow-up and study may help to more comprehensively assess treatment effects and long-term patient prognosis. The study did not also fully consider the impact of other medical conditions, medications or lifestyle factors that patients may have on the results.

CONCLUSION

Combined therapy of calcium dobesilate and candesartan demonstrates good efficacy in the treatment of proliferative diabetic retinopathy (PDR). It effectively inhibited the levels of TGF-β1, VEGF and IL-19 in the vitreous humor, contributing to improved outcomes for patients with PDR. Large-scale studies are needed to validate these findings and delve deeply into treatment mechanisms and long-term effects.

DECLARATIONS

Acknowledgements

None provided.

Funding

None provided.

Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors 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 them.

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