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Evaluating The Effects of Rivaroxaban Therapy on Proliferative Diabetic Retinopathy in Tertiary Healthcare Settings

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ABSTRACT

Background: Proliferative diabetic retinopathy (PDR) is a severe condition linked to diabetes that often causes vision loss around the world, due to abnormal blood vessels that can leak and weaken the retina. The available treatment methods are few. The study aimed to determine the effects of rivaroxaban therapy on PDR.

Methods: This randomized controlled, comparative study was conducted from May to October 2024 at Liaquat University of Medical and Health Sciences, Jamshoro. A total of 114 patients with PDR were recruited by using a non-probability consecutive sampling technique. Participants were randomly divided into two groups: Group A received 2.5 mg of rivaroxaban, and Group B received 5mg. Follow-up assessments were conducted on days 0, 30, 60, and 90 to monitor retinal changes. Data were analyzed using SPSS version 26.0 (released 2019, IBM Corp., Armonk, NY). Chi-square tests and independent t-tests were used. A p-value of < 0.05 was considered statistically significant.

Results: Group B resulted in better retinal conditions, including less blot hemorrhage ($p = 0.04$), venous caliber abnormalities ($p = 0.001$), intraretinal microvascular abnormalities (IRMA) ($p = 0.02$) and neovascularization at the optic disc (NVD) ($p = 0.00001$) and neovascularization elsewhere (NVE) ($p = 0.001$). Less impressive improvements were observed in Group A.

Conclusion: Taking 5 mg of rivaroxaban resulted in reduced diabetic retinopathy, showing that anticoagulant therapy may be effective for managing proliferative changes in diabetes. Considering the need for more data, it would be wise to have future trials in several medical centers.

Keywords: Rivaroxaban, Diabetic Retinopathy, Neovascularization, Anticoagulants, Type 2 Diabetes Mellitus.

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INTRODUCTION

Diabetic retinopathy is a frequent complication of diabetes mellitus and is a major cause of impaired and lost sight among working-age adults around the globe [1]. The spread of diabetic retinopathy is growing as more people get diabetes, mainly in low- and middle-income nations. PDR is the worst stage found in diabetic retinopathy, where new blood vessels grow abnormally on the retina and optic disc and threaten sight [2]. Because these blood vessels are quite frail, they easily burst, causing continual bleeding in the eye, scarring and the possible detachment of the retina, all contributing to eternal vision loss [3].

The main factors in the pathophysiology of PDR are long-lasting high blood sugar (hyperglycemia), vascular endothelial growth factor (VEGF) release from hypoxia, and both inflammation and oxidative stress [4]. The main treatments currently used for PDR are laser therapy, injections of anti-VEGF agents, and performing vitrectomy when the disease has advanced [5]. These treatments are often invasive, expensive, and not accessible easily in places with low resources. Some patients do not react as well to anti-VEGF drugs, so alternative or combined treatment options are needed [6]. Rivaroxaban belongs to the class of direct oral anticoagulants and figures in inhibiting factor Xa [7]. Although its main role is in stroke prevention for people with atrial fibrillation and venous thromboembolism, evidence suggests it may also lessen inflammation and blood clotting in small blood vessels [8]. Rivaroxaban could have a positive effect in patients with proliferation by boosting retinal blood flow and cutting down neovascularization caused by low oxygen levels [9,10].

Treatments for proliferative diabetic retinopathy require surgery, are costly, and work for only some individuals. Since rivaroxaban has anti-inflammatory and small blood vessel advantages, it is worthy of further evaluation as a medicine for treating the disease.

This study aimed to evaluate how rivaroxaban improves outcomes for patients with PDR by reviewing the results of 2.5 mg and 5 mg doses taken for three months. Study results might show new benefits of anticoagulation in diabetic eye disease and encourage it to be use in medical care if found to be effective.

METHODS

This study was conducted from May to October 2024 at the Department of Pharmacology and Ophthalmology, Liaquat University of Medical and Health Sciences Jamshoro (REC-759). The sample size was determined using OpenEpi version 3.0.0 (released 2013, Atlanta, GA,USA). Approximately 7–10% of diabetic patients are affected by proliferative diabetic retinopathy and the rate often increases when diabetes has been present for longer and blood sugar is not monitored well. A total of 114 participants were recruited using a non-probability consecutive sampling technique. All the patients were randomly divided into two groups: Group A (Rivaroxaban 2.5 mg, n = 57) and Group B (Rivaroxaban 5 mg, n = 57). Patients with PDR were included in the study to evaluate progression or regression to proliferative stages. Pregnant women, those with a history of coagulopathy, vitreous hemorrhage, sub-retinal hemorrhage, previous treatment for diabetic retinopathy by other means, hematological malignancies, and renal and hepatic impairment were excluded from the study. Patients fulfilling the inclusion criteria were selected for the study. Written consent was taken from all the participants of the study. All the diagnosed patients underwent a standard ophthalmoscopic procedure for the diagnosis of diabetic retinopathy by an ophthalmologist. Diabetic retinopathy was categorized as pre-proliferative retinopathy and proliferative retinopathy. All patients with bleeding diathesis were excluded by taking laboratory tests bleeding time (BT), clotting time (CT), Partial thromboplastin time (PTT), and Activated Partial thromboplastin time (APTT). They were followed up on day 0, 30, 60, and 90, respectively. All the data was recorded on a pre-designed proforma. On each visit, patients went for fundoscopy to check for regressive or progressive signs of diabetic retinopathy.

All the data were entered and analyzed using SPSS version 26.0 (released 2019, IBM Corp., Armonk, NY). Sample frequency and percentage were computed for the qualitative variables. The quantitative data were presented in the form of mean ± S.D. Age, gender, and duration of diabetes were calculated as effect modifiers. Chi-square test was applied, and a p-value < 0.05 was considered significant.

RESULTS

Table 1: Baseline Clinical Characteristics of Study Participants (n=114)

Variable	Group A (Rivaroxaban 2.5 mg)	Group B (Rivaroxaban 5 mg)	Test Value	p-value
Age (years, mean ± SD)	51.8 ± 14.2	51.6 ± 15.1	t = 0.11	0.91
Duration of Diabetes (years, mean ± SD)	6.7 ± 3.5	6.5 ± 3.9	t = 0.28	0.78
Fasting Blood Sugar (mg/dL, mean ± SD)	205.4 ± 98.1	203.8 ± 97.6	t = 0.11	0.91

HbA1c (%)	8.73 ± 0.61	8.70 ± 0.69	t = 0.28	0.78
Platelet Count (/mm³)	231,900 ± 214,500	233,849 ± 217,012	t = 0.07	0.94
Serum Creatinine (mg/dL)	0.41 ± 0.15	0.42 ± 0.17	t = 0.51	0.61

A total of 114 participants were randomly divided into two groups, 57 patients of Rivaroxaban 2.5 mg and 57 patients of 5 mg. The mean age of participants was 51.71 years with a standard deviation of 14.66 years. The age range was 64 years, between 22 and 86 years old. The baseline clinical characteristics of participants are shown in **Table 1**. Baseline demographic and clinical characteristics in Group A (Rivaroxaban 2.5 mg) and Group B (Rivaroxaban 5 mg) were compared using an independent samples t-test. Age, duration of diabetes, fasting blood sugar, HbA1c, platelet count or serum creatinine did not differ statistically. At baseline, the two groups were demographically and clinically comparable.

Table 2: Changes in Blot Hemorrhages Over Time

Time Point	Group	
	Rivaroxaban 2.5 mg (n=57)	Rivaroxaban 5 mg (n=57)
Day 0	44 (77.19%)	44(77.19%)
Day 30	44(77.19%)	43(75.43%)
Day 60	40(70.17%)	36(63.15%)
Day 90	37(64.91%)	21(36.84%)
P-value	**0.04**	

Reduction of blot hemorrhages at Days 0, 30, 60 and 90 was assessed using chi-square test in both groups. Group B (5 mg) showed significant reduction observed by Day 90 vs Group A (p-value: 0.04). Blot hemorrhages are reduced more over time by rivaroxaban 5 mg as shown in **Table 2**.

Table 3: Abnormalities in Venous Caliber Over Time

Time Point	Group	
	Rivaroxaban 2.5 mg (n=57)	Rivaroxaban 5 mg (n=57)
Day 0	21(36.84%)	21(36.84%)
Day 30	21(36.84%)	19(33.33%)
Day 60	18(31.57%)	10(17.54%)
Day 90	17(29.82%)	3(5.26%)
P-value	**0.001**	

Venous caliber abnormalities across 90 days were evaluated using chi-square test. The reduction was observed in group B from 36.84% to 5.26 by Day 90 (**p-value:** 0.001). Venous caliber abnormalities were significantly improved with higher dose rivaroxaban as shown in **Table 3**.

Table 4: Incidence of IRMA Over Time

Time Point	Group	
	Rivaroxaban 2.5 mg (n=57)	Rivaroxaban 5 mg (n=57)
Day 0	12(21.05%)	12(21.05%)
Day 30	12(21.05%)	10(17.54%)
Day 60	12(21.05%)	7(12.28%)
Day 90	9(15.78%)	5(8.77%)
P-value	**0.02**	

IRMA changes over 90 days were assessed using the chi‡square test. By Day 90, there was a significant reduction in Group B IRMA incidence (p=0.02). Rivaroxaban 5 mg has a favorable effect on reducing the IRMA at follow-up, as shown in **Table 4**.

Table 5: New Active Vessels at Optic Disc Over Time

Time Point	Group	
	Rivaroxaban 2.5 mg (n=57)	Rivaroxaban 5 mg (n=57)
Day 0	11(19.29%)	11(19.29%)
Day 30	11(19.29%)	8(14.03%)
Day 60	10(17.54%)	7(12.28%)
Day 90	9 (15.78%)	3(5.26%)
P-value	**0.00001**	

Formation of new active vessels at the optic disc was monitored using chi square test. Group B demonstrated a significant reduction from 19.29% at baseline to 5.26% at Day 90 (**p-value:** < 0.00001). High-dose rivaroxaban markedly reduces optic disc neovascularization as shown in **Table 5**.

Table 6: New Active Vessels Elsewhere Over Time

Time Point	Group A	Group B
	Rivaroxaban 2.5 mg (n=57)	Rivaroxaban 5 mg (n=57)
Day 0	10(17.54%)	10(17.54%)
Day 30	10(17.54%)	9(15.78%)
Day 60	10(17.54%)	5(8.77%)
Day 90	8(14.03%)	3(5.26%)
P-value	**0.001**	

New vessel formation elsewhere in the retina was evaluated by a chi-square test. Group B had a significant decrease to 5.26% at Day 90 as compared to 14.03% in Group A (**p-value: 0.001**). Rivaroxaban 5 mg significantly limits peripheral retinal neovascularization as shown in **Table 6.**

DISCUSSION

This study evaluated the effect of rivaroxaban therapy at different doses (2.5 mg and 5 mg) in people with PDR. It was demonstrated that a higher dose (5mg) of rivaroxaban strongly decreased signs of diseases linked with PDR. The rate of improvement in blot hemorrhages, venous caliber abnormalities, IRMA, and neovascularization at the optic disc was greater for patients treated with 5 mg over the 90 days compared to those given 2.5 mg each day. It appears that rivaroxaban, given in higher doses, may support retinal blood vessels and reduce the growth of new blood vessels, giving a possible way to treat PDR.

These findings are consistent with earlier studies, which suggested that anticoagulants could play a role in treating retinal vascular conditions. Evidence showed that when blood clots more easily, diabetic retinopathy can include retinal damage, inflammation and expansion of blood vessels [11,12]. A direct Factor Xa inhibitor (rivaroxaban) not only prevents thrombus formation but may also influence endothelial function, block inflammatory cytokines and enhance retinal perfusion [13,14]. Factor Xa inhibition can suppress VEGF expression and neovascular responses under hypoxic conditions, according to animal studies [15,16].

A systemic, non-invasive alternative for the treatment of PDR compared to other traditional treatments like laser photocoagulation and intravitreal anti-VEGF injections is rivaroxaban. Current treatments consist of laser therapy, which is successful but can damage healthy retina nearby; whereas anti-VEGF agents involve frequent intraocular injections and are prohibitively costly and have patient compliance issues [17,18.] Therefore, the oral route of rivaroxaban may represent a more patient-friendly adjunct or alternative, especially in resource-poor areas [19].

While the molecular mechanism of action underlying rivaroxaban's benefit is linked to its effects on the coagulation cascade and endothelial homeostasis, these results support biological plausibility for rivaroxaban's benefits in these conditions [20]. Increased expression of pro-coagulant factors, platelet activation, and impairment in fibrinolysis associated with hyperglycemia in diabetic states promote a

medium conducive to microthrombosis and capillary non-perfusion [21,22]. In addition to the reduction of clot formation, inhibition of Factor Xa by rivaroxaban also reduces monocyte activation and vascular inflammation, the main contributors to DR progression [23].

The results are significant because eye doctors will have an opportunity to reduce progression to vision-threatening stages, decrease the frequency of invasive ocular procedures, and increase patient quality of life [24]. Systemic anticoagulation, however, is associated with appreciable bleeding risks, for which judicious patient selection and monitoring are required [25].

A number of limitations existed with this study. Generally, however, the use of a non-probability consecutive sampling technique limits generalizability. Furthermore, the single-centered design and shorter follow-up period (90 days) restrict evaluation of longer outcomes and safety. The only two doses tested were without a placebo or a comparison group to the standard of care. Additional multicenter randomized trials with longer follow-up and with a larger sample size are warranted and these trials should be compared with established therapies, e.g., anti-VEGF agents. Such investigations would also improve clinical understanding of detecting biomarkers and imaging tools that monitor the microvascular changes associated with the use of an anticoagulant.

CONCLUSION

Taken together, preliminary evidence is provided for rivaroxaban, especially at a 5 mg dose, as a potential adjunctive therapy for PDR. Over a 90-day treatment time period, significant improvements in retinal hemorrhages, venous abnormalities, IRMA, and neovascularization were noted. These findings indicate a potential for systemic anticoagulation to help stabilize the retinal microvasculature and thereby limit progression of the disease. Despite the promise of these results, however, more extended, multicenter trials will be necessary before incorporating rivaroxaban into the standard ophthalmic care of this condition.

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CONFLICT OF INTEREST

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ETHICAL APPROVAL

This study was conducted from May to October 2024 at the Department of Pharmacology and Ophthalmology, Liaquat University of Medical and Health Sciences, Jamshoro (REC-759).

AUTHORS' CONTRIBUTION

All authors contributed equally as per ICMJE.

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