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Efficacy and Safety of Combination of Intravitreal Anti-Vegf Injections with Subcutaneous Low-Molecular-Weight Heparin in Retinal Venous Occlusive Diseases

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Abstract

Background: Retinal venous occlusion (RVO) is the second most common vascular retinopathy after diabetic retinopathy.

Objective: To find out the safety and efficacy of combination of intravitreal anti-VEGF injections with subcutaneous low molecular weight heparin in retinal vascular occlusive disorders.

Methods: This study included 100 patients with RVO who were divided into two groups. The study group included 50 subjects who received both Intravitreal Anti-VEGF (Ranibizumab) and Subcutaneous LMWH (Enoxaparin) injections .The control group consisted 50 patients who received only Intravitreal Anti-VEGF. Best-corrected visual acuity (BCVA) and uncorrected visual acuity was documented before and after treatment. Optical coherence tomography was used to evaluate central macular thickness (CMT) at baseline and after treatment.

Results: This study included 100 patients with Retinal Venous Occlusion. At baseline, both groups had comparable mean CMT values. Following treatment, there was a significant reduction in CMT in both the groups, but post-treatment CMT was significantly lower in case group (233.02 µm) compared to the control group (260.48 µm). Post-treatment at 1 month, Best Corrected Visual Acuity improved more significantly in the case group compared to controls.

Conclusion: The addition of low molecular weight heparin to intravitreal anti VEGF significantly enhance treatment efficacy, particularly in terms of anatomical and visual outcomes.

Keywords: Central Macular Thickness**,** Diabetic Retinopathy, Low Molecular Weight Heparin, Retinal venous occlusion, Optical coherence tomography.

Introduction

Worldwide, retinal diseases are important causes of visual impairment predominantly in middle aged and elderly individuals [1,2]. Retinal venous occlusion (RVO) is the second most common vascular retinopathy after diabetic retinopathy [3,4]. Patients with retinal venous occlusion generally presents with sudden, unilateral, painless loss of vision[5,6]. Its prevalence varies between 0.6-4.6% in patients aged 80 years or more. Risk factors include hypertension, hyperlipidemia, raised blood glucose levels and smoking.[7]

Long-term complications include substantially reduced vision, rubeosis iridis, leading to neovascular glaucoma. Various treatment modalities have been investigated including grid laser photocoagulation, ticlopidine, hemodilution, streptokinase and angiogenesis inhibitors such as bevacizumab.[8,9]

Bevacizumab is an anti-VEGF agent that was primarily introduced for the management of exudative age-related macular degeneration, can also be used to prevent and treat retinal neovascularization.[10] Research shows that bevacizumab and ranibizumab are effective in management of retinal venous occlusion.[11] Studies show that there is improvement in visual acuity six months after treatment with bevacizumab and reduces the chances of side effects, including disturbances in vision, abnormalities in fundus fluorescein angiography and neovascularisation.[12] Use of LMWH is safe as it does not increase the risk of vitreous hemorrhage. [13]

Enoxaparin can be injected subcutaneously twice daily in patients with retinal venous occlusions, resulting in a decrease in retinal and orbital edema, hemorrhage and improvement in visual acuity.[14]

Low-molecular-weight heparin is successful for management of Branch retinal venous occlusion (BRVO) as BRVO is a venous thromboembolic disorder. It causes increase in visual acuity with minimal increase of risk of vitreous hemorrhage.

The combination of anti-VEGF drugs and low molecular weight heparin can substantially reduce vascular leakage and thrombosis in venous occlusive disorders. Anti-VEGF drugs inhibit vascular permeability induced by vascular endothelial growth factors and neovascularization, thus reducing macular edema. Heparin has anticoagulant properties that prevent further venous occlusion and improves retinal blood flow. LMWH has anti-inflammatory activity that improve visual acuity and reduce the need for anti-VEGF injections. This combined treatment thus has a long lasting therapeutic role.

Thus the present study was done to find out efficacy of the combination of intravitreal anti-VEGF injections with subcutaneous low-molecular-weight heparin in retinal vascular occlusive disorders.

Materials and Methods

It was a prospective interventional study which was initiated after due approval from the Institutional Ethics Committee. Informed and written consent was deciphered from all the participants. The study strictly confirmed adherence to the Helsinki Declaration performed in a randomly selected sample of 100 patients with retinal venous occlusion attending outpatient Ophthalmology department in a tertiary care hospital. These patients were equally divided into two groups of cases and control comprising 50 patients in each group. All participants underwent a comprehensive Ophthalmological examination, including a detailed questionnaire (including age, sex, general, and ocular disease history), uncorrected and best corrected visual acuity, refractive error assessment, slit-lamp examination

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of the anterior segment, fundus examination after pupillary dilation using Indirect Ophthalmoscope. Ophthalmological examination of the eyelid, globe, pupillary reflex, and lens was performed by an experienced ophthalmologist. The study group included 50 subjects who received both Intravitreal Anti-VEGF (Ranibizumab) and Subcutaneous LMWH (Enoxaparin) injections. The control group consisted 50 patients who received only Intravitreal Anti-VEGF (Ranibizumab) injection. Optical Coherence Tomography scans were done which was used to evaluate central macular thickness at baseline and after treatment.

Statistical Analysis

The statistical analysis was performed with SPSS version 23.0. The data was demonstrated in the form of mean (standard deviation) and percentage (%). The chi-square test was used to compare categorical variables, while the independent t-test was used to assess discrete variables between both groups. A p-value of 0.05 was considered statistically significant.

Results

Table 1: Distribution of Types of Retinal Vein Occlusion (RVO) Among Case and Control Groups

Type of Retinal Vein Occlusion (RVO)	Case (n=50)		Control (n=50)		Chi Sq.	p-Value
	n	%	n	%		
Superotemporal BRVO	25	50.00	15	30.00	7.15	0.307
Inferotemporal BRVO	11	22.00	13	26.00		
Central Retinal Vein Occlusion	5	10.00	5	10.00		
Inferior Hemiretinal Vein Occlusion	0	0.00	3	6.00		
Ischaemic CRVO	4	8.00	7	14.00		
Non ischaemic CRVO	3	6.00	3	6.00		
Superior hemiretinal vein occlusion	2	4.00	4	8.00		

Table 1 shows the distribution of various types of retinal vein occlusion (RVO) in the case and control groups. The most common type in both groups was superotemporal branch retinal vein occlusion (BRVO), observed in 50% of the case group and 30% of the control group. Other subtypes such as inferotemporal BRVO, ischemic and non-ischemic CRVO, and hemiretinal occlusions were distributed across both groups in smaller proportions.

Table 2: Comparison of Central Macular Thickness (CMT) Between Case and Control Groups

	Case (n=50)		Control (n=50)		t	p-Value
	Mean	±SD	Mean	±SD		
Baseline Central Macular Thickness (CMT) (µm)	470.30	93.29	472.28	87.49	-0.11	0.913
Post-injection Central macular thickness(µm)	233.02	28.88	260.48	54.32	-3.16	0.002

Table 2 compares the central macular thickness (CMT) measured by OCT at baseline and post-treatment between the case and control groups. At baseline, both the groups had comparable mean CMT values (470.30 µm in case vs. 472.28 µm in control), and the difference was not statistically significant (p = 0.913), indicating similar starting points in terms of severity of macular edema.

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Following treatment, there was a significant reduction in CMT in both the groups, but the mean post-treatment CMT was significantly lower in the case group (233.02 µm) compared to the control group (260.48 µm), with a statistically significant difference (t = -3.16, p = 0.002).

Table 3: Comparison of Visual Acuity Outcomes between Case and Control Groups

UCVA		Case (n=50)		Control (n=50)		Chi Sq.	p-Value
		n	%	n	%		
Pre-Treatment	6/6 to 6/9	0	0.00	0	0.00	3.99	0.262
	6/12 to 6/18	0	0.00	0	0.00		
	6/24 to 6/36	10	20.00	5	10.00		
	≤6/60	36	72.00	41	82.00		
	FC1Ft	3	6.00	1	2.00		
	FCCF	1	2.00	3	6.00		
Visual Acuity at Follow-up (LogMAR/Snellen)	6/6 to 6/9	0	0.00	0	0.00	6.78	0.034
	6/12 to 6/18	15	30.00	7	14.00		
	6/24 to 6/36	20	40.00	16	32.00		
	≤6/60	15	30.00	27	54.00		
Post-injection Visual Acuity	6/6 to 6/9	16	32.00	3	6.00	15.17	0.004
	6/12 to 6/18	19	38.00	19	38.00		
	6/24 to 6/36	5	10.00	12	24.00		
	≤6/60	10	20.00	13	26.00		
	Not Improved	0	0.00	3	6.00		

Table 3 shows the uncorrected visual acuity (UCVA), follow-up acuity, and post-injection visual outcomes among case and control groups:

Pre-treatment UCVA was comparable between both the groups (p = 0.262), with the majority of patients having poor vision (≤6/60), indicating no baseline visual disparity. At follow-up, visual acuity improved in both groups, but significantly more patients in the case group reached 6/12–6/18 or better compared to controls. The Chi-square test showed a significant difference (p = 0.034), suggesting that combination therapy with anti-VEGF and LMWH was more effective in improving vision over time. Post-injection visual acuity demonstrated a highly significant difference between groups (Chi Sq. = 15.17, p = 0.004). Notably, 32% of patients in the case group achieved 6/6 to 6/9 compared to only 6% in the control group. Additionally, no patient in the case group showed "Not Improved" status, whereas 6% in the control group did not show any improvement.

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Table 4: Comparison of Best Corrected Visual Acuity (BCVA) Between Case and Control Groups

BCVA		Case (n=50)		Control (n=50)		Chi Sq.	p-Value
		n	%	n	%		
Pre-Treatment	6/6 to 6/9	0	0.00	0	0.00	6.34	0.096
	6/12 to 6/18	8	16.00	1	2.00		
	6/24 to 6/36	7	14.00	10	20.00		
	≤6/60	20	40.00	24	48.00		
	Not Improved	15	30.00	15	30.00		
Post Treatment at 1 month	6/6 to 6/9	3	6.00	0	0.00	13.32	0.010
	6/12 to 6/18	18	36.00	9	18.00		
	6/24 to 6/36	17	34.00	17	34.00		
	≤6/60	10	20.00	12	24.00		
	Not Improved	2	4.00	12	24.00		

Table 4 compares the Best Corrected Visual Acuity (BCVA) between the case and control groups before and after treatment. Pre-treatment, there was no statistically significant difference in BCVA between the two groups (Chi-square = 6.34, p = 0.096). In the case group, 8 patients (16.00%) had BCVA between 6/12 and 6/18, 7 (14.00%) had 6/24 to 6/36, 20 (40.00%) had ≤6/60 vision, and 15 (30.00%) showed no improvement. Similarly, in the control group, 1 patient (2.00%) had 6/12 to 6/18, 10 (20.00%) had 6/24 to 6/36, 24 (48.00%) had ≤6/60 vision, and 15 (30.00%) did not show any improvement. Post-treatment at 1 month, BCVA improved more significantly in the case group compared to controls (Chi-square = 13.32, p = 0.010). In the case group, 3 patients (6.00%) achieved 6/6 to 6/9 vision, 18 (36.00%) achieved 6/12 to 6/18, and only 2 (4.00%) showed no improvement. In contrast, none of the patients in the control group reached 6/6 to 6/9, only 9 (18.00%) achieved 6/12 to 6/18, and 12 (24.00%) had no improvement. This significant post-treatment improvement in the case group suggests that combination therapy (anti-VEGF with LMWH) may lead to better visual recovery compared to anti-VEGF alone.

Table 5: Post-Injection OCT and Clinical Outcomes among Case and Control Groups

		Case (n=50)		Control (n=50)		Chi Sq.	p-Value
		n	%	n	%		
Post-injection OCT	Done	50	100.00	50	100.00	-	-
Macular Edema	Yes	1	2.00	15	30.00	12.57	*<0.001*
Retinal Hemorrhage Resolution	yes	49	98.00	46	92.00	0.84	*0.362*
	partial	1	2.00	4	8.00		
Neovascularization	Yes	0	0.00	0	0.00	-	-
Ocular Side Effects (Endophthalmitis,	Yes	0	0.00	0	0.00	-	-

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Vitreous Hemorrhage, Retinal Tear, etc.)							
Hematoma(at site of subcutaneous injection LMWH)	Yes	3	6.00	0	0.00	1.37	0.241
Patient lost to follow up	Yes	2	4.00	2	4.00	0.00	1.000

Table 5 presents the findings of post-injection Optical Coherence Tomography (OCT) and clinical outcomes in both the case and control groups following intravitreal therapy. All patients in both the case group and control group underwent post-injection OCT, ensuring complete follow-up for imaging evaluation.

One of the key findings was the presence of macular edema, which was significantly lower in the case group—only 1 patient (2.00%)—compared to 15 patients (30.00%) in the control group. This difference was statistically significant, with a Chi-square value of 12.57 and a p-value < 0.001, indicating a strong association between the intervention used in the case group and reduced incidence of post-treatment macular edema.

Resolution of retinal hemorrhage was also more favorable in the case group, where 49 patients (98.00%) showed complete resolution compared to 46 patients (92.00%) in the control group. Although this outcome was clinically better in the case group, the difference was not statistically significant (Chi-square = 0.84, p = 0.362).

No neovascularization or ocular side effects (such as endophthalmitis, vitreous hemorrhage, or retinal tears) were observed in either group, highlighting the overall safety of the procedure. Hematoma at the site of subcutaneous LMWH injection was reported in 3 patients (6.00%) in the case group and in none of the controls, though this difference was not statistically significant (Chi-square = 1.37, p = 0.241). Additionally, patient loss to follow-up was equal in both groups at 4.00%, and this showed no statistical difference (p = 1.000).

Discussion

The present study was undertaken in patients of retinal venous occlusion attending outpatient department in a tertiary care hospital. The study group included 50 subjects who received both Intravitreal Anti-VEGF (Ranibizumab) and Subcutaneous LMWH (Enoxaparin) injections. The control group consisted of 50 patients who received only Intravitreal Anti-VEGF (Ranibizumab) injection. In our study, the mean age of patients in case group was 60.64 ± 6.83 years, while in control group it was 58.30 ± 7.60 years. The difference between the two groups was not found to be statistically significant (t = 1.62, p = 0.109). Age has been considered as an important factor in the prognosis of retinal venous occlusive disorders. Rogers et al. (2010)[15] and Ho et al. (2016)[16] observed increased incidence of retinal venous occlusive disorders among elderly, as their blood vessels become stiffer and their blood vessel lining gets worsen with age.

In our study, supero-temporal branch retinal vein occlusion (BRVO) was the most common subtype in both the groups—50% in the case group and 30% in the control group. Other types, like inferotemporal BRVO, central retinal vein occlusion (CRVO), and hemiretinal occlusions were less prevalent and did not showed any significant differences among the two groups.

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In our study, post-treatment central macular thickness (CMT) was significantly lower in the combination group (233.02 μm) compared to that of the control group (260.48 μm), with a p-value of 0.002. The result indicates that response to combination therapy was better as compared to single therapy. Reduction in CMT is a key marker for efficacy of treatment in RVO. Studies by Nguyen et al. (2012)[17] and Campochiaro et al. (2011)[18] showed that using only ranibizumab greatly lowers CMT; but our results indicate that adding LMWH might make this effect even stronger. Steigerwalt et al. (2008)[14] and Lazo-Langner et al. (2010)[19] showed betterment in perfusion of retina and reduction in central macular thickness by LMWH.

In our study, there was a significant improvement in visual acuity in the combination group. 32% patients in cases achieved UCVA of 6/6–6/9 post treatment as compared to only 6% in the control group (Chi Sq. = 15.17, p = 0.004). However both the groups had comparable baseline Best Corrected Visual Acuity (BCVA), with no statistically significant difference observed pre-treatment (Chi-square = 6.34, p = 0.096). The case group were given a combination therapy of intravitreal injection of anti VEGF with subcutaneous injection of low molecular weight heparin (LMWH), while control group received only intravitreal anti-VEGF therapy. At 1-month follow-up, the case group showed significantly better visual improvement (Chi-square = 13.32, p = 0.010). Specifically, more patients in the case group achieved higher levels of visual acuity, and fewer remained unimproved compared to the control group. These findings suggest that the addition of LMWH to anti-VEGF therapy may offer superior visual recovery in patients with retinal venous occlusive disorder. These findings are similar with Steigerwalt et al. (2008)[14], who reported vision improvement in 7 out of 8 patients with RVO treated with enoxaparin. Valeriani et al. (2023)[20] also found that anticoagulants led to higher BCVA improvement rates than antiplatelet therapy.

In our study**,** only 2% of patients in the combination group had ongoing macular edema, while 30% in the control group did (Chi Sq. = 12.57, p < 0.001), showing that LMWH is quite effective in resolution of macular edema. Resolution of retinal hemorrhage was slightly better in the case group (98%) versus the control group (92%), though this was not statistically significant (p = 0.362). We may attribute this contradictory finding to temporal assessment variability or differing criteria for defining resolution. Steigerwalt et al. (2008)[14] documented that use of LMWH resolved hemorrhage and edema after 2–19 weeks, which might explain our lower complete resolution rate if assessed prematurely. However, the significant difference in how quickly edema improved shows that LMWH is effective in treating fluid buildup in the retina, especially when used with anti-VEGF agents.

In our study**,** 80% in the case group and 74% in the control group had normal anterior segment findings—. Cataractous changes and exotropia were present in a few patients, with no statistically significant difference (Chi Sq. = 6.40, p = 0.269). Pupillary abnormalities such as RAPD were noted in 12% of cases and 16% of controls. These findings are in correspondence with those of Ho et al. (2016), who noted minimal correlation between anterior segment findings and RVO outcomes.

Our results show increase in benefit of combination therapies in management of retinal venous occlusive disorders. Although anti-VEGF alone has been proven effective in studies like BRAVO and CRUISE, it requires many injections and its effectiveness can level

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off, which are drawbacks. LMWH may enhance anti-VEGF efficacy by addressing the thrombotic component of RVO. As Formica et al. (2021)[21] and Uludag et al. (2024) suggest, future advancements might include methods like hydrogels, biosimilars, and gene therapy to improve how long treatments last and how well they work. Until such technologies become widely accessible, combining anti-VEGF with safe systemic agents like LMWH represents a practical and effective approach in real-world settings.

Conclusions

Addition of LMWH to intravitreal injection of anti-VEGF significantly enhance treatment efficacy, particularly in terms of anatomical and visual outcomes. Adjunctive LMWH therapy provide synergistic benefits when combined with anti-VEGF in managing RVOs, due to its additional antithrombotic and anti-inflammatory effects. Given its favourable safety profile and significant improvement in visual outcomes, combination therapy could be considered as more effective therapeutic strategy in the clinical management of RVOs.

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