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ORIGINAL ARTICLE

Comparison of efficacy of subconjunctival bevacizumab and diathermy cauterization in corneal neovascularization.

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ABSTRACT… Objective: To compare the efficacy of subconjunctival bevacizumab injection vs diathermy cautery in treatment of corneal neovascularization. **Study design:** Randomized controlled trial. **Setting:** Eye Unit-3, Institute of Ophthalmology, Mayo Hospital, Lahore. **Period:** September'24 to February'25. **Methods:** A total of 100 patients with superficial CNV were randomized into two equal groups. Group A received a single subconjunctival injection of bevacizumab (2.5 mg/0.1 mL)., while Group B received diathermy cauterization Efficacy was defined as ≥50% regression of neovessels after 4 weeks. Visual acuity, complication rates, and demographic variables were analyzed using appropriate statistical tests. **Results:** Efficacy was significantly higher in the bevacizumab group (48.0%) compared to the Diathermy group (24.0%) (p = 0.012). Complication rates were lower in the bevacizumab group (14.0%) than in the diathermy group (28.0%), though not statistically significant. Subgroup analysis revealed higher efficacy in females treated with bevacizumab (50.0%) versus diathermy (16.7%, p = 0.021). **Conclusion:** Subconjunctival bevacizumab is more effective and safer than Diathermy cauterization for the treatment of superficial corneal neovascularization. It offers a practical solution and may be considered the preferred first-line option in similar clinical scenarios.

Key words: Anti-VEGF, Bevacizumab, Corneal Neovascularization, Diathermy Cauterization, Randomized Controlled Trial, Superficial Corneal Vessels.

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INTRODUCTION

Corneal neovessels (NV) is a sight-threatening condition that affects about 1.4 million people every year.[1] Corneal neovascularization is divided into three categories as superficial, pannus, and deep stromal vascularization. Etiology mainly includes infections (bacterial, fungal, viral), burns (chemical or thermal), trauma, and immunological.[1,2] These conditions cause upregulation of angiogenic cytokines that enter stromal spaces causing degradation of extracellular matrix and formation of neovessels.[3] Corneal neovessels are examined on slit lamp using red-free filter. New methods of examination include Fluorescein, Indocyanine Green Angiography (ICGA), and Optical Coherence Tomography (OCT) which are new modalities but unfortunately are not cost-effective and easily accessible in our country.[4,5]

Management of the corneal neovascularization includes medical, surgical, laser (diode), and photodynamic treatment methods. Topical steroids and NSAIDs (Non-Steroidal Anti-Inflammatory Drugs) need to be administered within 24 hours of initial insult of cornea to prevent corneal NV.[1,6] Monoclonal anti-vascular endothelial growth factor (VEGF) antibodies like ranibizumab and bevacizumab, when administered through subconjunctiva, help in reducing corneal NV.[7-9] Metalloproteinase (MP) inhibitors like doxycycline can also be used in combination with corticosteroids topically to inhibit neovascularization. Surgical management for corneal NV includes photodiathermy, diathermal cautery, and laser ablation. Cauterization of feeding vessels with a diathermy is cost-effective with a high success rate.

Adnane et al. compared outcomes of different treatment modalities in corneal neovascularization and reported that disappearance of neovascularization was observed in 60% of patients in the diathermy cauterization group, compared to 35% of patients in the subconjunctival bevacizumab group. Complications including subconjunctival hemorrhage were reported in 25% of patients of

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the subconjunctival bevacizumab group and 15% of patients of the diathermy cauterization group.[10] Elbaz et al. studied outcomes of corneal laser cauterization followed by subconjunctival bevacizumab and reported that it was associated with disappearance of neovascularization in 89% of patients.[11] In 2020, researchers at the University of Cologne, Germany, studied the effect of supplemental anti-VEGF therapy following a fine needle diathermy (FND) cautery. The group treated with FND monotherapy had no recurrent corneal NV on the 3rd day after the treatment; however, the same group had recurrent corneal NV on the 7th and 14th day after monotherapy. The group with supplemental anti-VEGF with FND had no recurrent corneal NV on the 3rd, 7th, and 14th day post treatment.[12] A 2017 review study conducted at the University of Medical Sciences, Iran, on therapeutic approaches for corneal neovascularization concluded that anti-VEGF agents were effective in the treatment of superficial corneal neovessels, whereas surgical and diode therapy proved beneficial for treating deep stromal vessels.[13]

No local data is available regarding the effective treatment options for corneal neovascularization in terms of time-saving and cost-effectiveness. The purpose of this study is to compare the effectiveness of two management techniques, i.e diathermy cauterization and subconjunctival anti-VEGF (vascular endothelial growth factor) (Bevacizumab) in terms of treatment outcomes and patient benefit for corneal NV. This study aims to establish better practice guidelines among fellow ophthalmologists.

METHODS

This randomized controlled trial was conducted at Eye Unit-3 of the Institute of Ophthalmology, Mayo Hospital, Lahore, over a period of six months September'24 to February'25 following the approval of the synopsis from the CPSP and Institutional Review Board (Ref. No:320, Dated: 30-08-2024). The study aimed to evaluate and compare the efficacy of two treatment modalities for corneal neovascularization subconjunctival Bevacizumab injection and diathermy cauterization. A total of 100 patients were included in the trial, with 50 patients allocated to each treatment group. The sample size was calculated using the CPSP endorsed Sample Size Calculator, based on a 10% level of significance and 80% test power. The expected efficacy rate for Bevacizumab was assumed to be 35%, while for diathermy cautery it was 60%.[10]

Participants were selected using a non-probability consecutive sampling method. Individuals eligible for inclusion were aged between 18 and 40 years, of either gender, and had at least one or two superficial corneal neovessels greater than 2 mm in length, extending from the limbus and involving a minimum of two clock hours of the superficial layers of cornea. Patients who consented to undergo the treatment and agreed to attend follow-up visits were enrolled. Exclusion criteria comprised individuals with a recent history of ischemic heart disease, anterior staphyloma, scleral thinning, or severe dry eye syndrome.

Upon obtaining informed consent, each participant underwent a thorough ophthalmic examination, which included best corrected visual acuity (BCVA) assessment and slit lamp evaluation under red-free illumination to count the number of corneal neovessels. Patients were then randomly assigned into one of the two treatment groups through the lottery method to ensure unbiased allocation. Group B patients received diathermy cauterization using bipolar electrocautery, whereas Group A patients were administered a subconjunctival injection of Bevacizumab at a dose of 2.5 mg/0.1 mL using a 27-gauge needle under sterile conditions. All procedures were carried out under topical anesthesia by the same ophthalmologist to maintain consistency across interventions.

Participants were followed up after four weeks to assess the treatment outcomes. During follow up visits, the same slit lamp-based examination was repeated to evaluate any changes in the number of neovessels, using the defined grading criteria. The primary efficacy outcome was defined as a >50% reduction in the number of pretreatment superficial corneal neovessels longer than 2 mm in at least two clock hours of the cornea. Any complications associated with the treatments were also noted.

Statistical computations were performed using IBM SPSS Statistics version 26.0. Continuous variables

such as age and BCVA were expressed as mean ± standard deviation, and categorical data, including gender and clinical outcomes, were displayed as frequencies and percentages. The Shapiro–Wilk test was used to verify normality, which was not satisfied for the continuous variables. Hence, the Mann–Whitney U test was used for intergroup comparisons of these variables. The Chi-square test was employed for categorical data. A significance level of $p < 0.05$ was adopted.

RESULTS

The mean age of participants in the bevacizumab group was 29.92 ± 6.88 years, while it was 28.64 ± 6.00 years in the other group. Although the age was slightly higher in the bevacizumab group, ($U = 1113.5$, $Z = –0.942$, $p = 0.346$). Similarly, the mean baseline BCVA was 0.53 ± 0.26 logMAR in Group A and 0.49 ± 0.26 logMAR in Group B. ($U = 1146.5$, $p = 0.475$). After treatment, the mean BCVA improved to 0.39 ± 0.24 logMAR in Group A and 0.37 ± 0.22 logMAR in Group B. ($U = 1191.5$, $p = 0.686$), suggesting both treatments had comparable effects on visual improvement. (Table-I)

TABLE-I

Descriptive and mann–whitney u test results

Variable	Group A (Mean ± SD)	Group B (Mean ± SD)	P-Value (Mann–Whitney)
Age (years)	29.92 ± 6.88	28.64 ± 6.00	0.346
BCVA Baseline (logMAR)	0.53 ± 0.26	0.49 ± 0.26	0.475
BCVA Follow-up (logMAR)	0.39 ± 0.24	0.37 ± 0.22	0.686

Efficacy, defined as ≥50% disappearance of neovascularization, was significantly higher in the bevacizumab group (48.0%) compared to the Diathermy group (24.0%, $p = .012$). There was no statistically significant difference between groups in gender distribution ($p = .224$), grade of neovascularization at baseline or follow-up ($p = .873$ and .846, respectively), partial regression ($p = .509$), or BCVA improvement ($p = .558$). but this difference did not reach statistical significance ($p = .086$). (Table-II)

The relationship between treatment efficacy and patient age was examined in two strata: 18–30 years and 31–40 years. Among patients aged 18–30, efficacy was achieved in 50.0% of those treated with bevacizumab injection compared to 27.6% in the Diathermy group. Although this difference showed a trend toward significance, it did not reach statistical significance ($p = 0.088$). Similarly, in the 31–40 age group, 45.8% of patients in the bevacizumab group achieved efficacy, again approaching but not reaching statistical significance ($p = 0.057$).

When stratified by baseline grade of corneal neovascularization, patients with Grade I disease showed better efficacy in the bevacizumab group (43.5%) than in the Diathermy group (18.2%), ($p = 0.067$). Similar patterns were observed in Grade II and Grade III subgroups, where the bevacizumab group consistently showed higher efficacy percentages, but without statistical significance ($p = 0.219$ and $p = 0.168$, respectively). Finally, stratification by presence of complications demonstrated a statistically significant difference in efficacy among those without complications ($p = 0.008$). In this group, 51.2% of patients in the bevacizumab group achieved efficacy compared to 22.2% in the Diathermy group. Among patients with complications, the rates of efficacy were identical between groups (28.6%). ($p = 1.000$). (Table-III)

DISCUSSION

Corneal neovascularization (NV) is a vision-threatening condition resulting from inflammatory, infectious, or traumatic insults, leading to abnormal vascular proliferation in the corneal stroma. Our results demonstrate that bevacizumab was significantly more effective than other group in achieving >50% regression of neovessels (48.0% vs. 24.0%; $p = 0.012$), with fewer reported complications (14.0% vs. 28.0%).

The mean age of participants was similar between groups (29.92 ± 6.88 years in the bevacizumab group vs. 28.64 ± 6.00 years in the other group; $p = 0.346$), indicating demographic comparability. Stratified analysis showed that younger patients (18–30 years) responded better to bevacizumab (50.0%) compared to diathermy (27.6%), although the difference was not statistically significant ($p = 0.088$).

TABLE-II

Comparison of categorical variables between groups

Variable	Group	Bevacizumab (n, %)	Diathermy (n, %)	Total (n, %)	P-Value
Gender	Male	32 (64.0%)	26 (52.0%)	58 (58.0%)	.224
	Female	18 (36.0%)	24 (48.0%)	42 (42.0%)	
Grade Baseline	Grade I	23 (46.0%)	22 (44.0%)	45 (45.0%)	.873
	Grade II	19 (38.0%)	18 (36.0%)	37 (37.0%)	
	Grade III	8 (16.0%)	10 (20.0%)	18 (18.0%)	
Grade Followup	Grade I	30 (60.0%)	31 (62.0%)	61 (61.0%)	.846
	Grade II	18 (36.0%)	16 (32.0%)	34 (34.0%)	
	Grade III	2 (4.0%)	3 (6.0%)	5 (5.0%)	
Efficacy	Yes	24 (48.0%)	12 (24.0%)	36 (36.0%)	.012
	No	26 (52.0%)	38 (76.0%)	64 (64.0%)	
	No	37 (74.0%)	34 (68.0%)	71 (71.0%)	
Improved BCVA	Yes	49 (98.0%)	48 (96.0%)	97 (97.0%)	.558
	No	1 (2.0%)	2 (4.0%)	3 (3.0%)	
Complications	Yes	7 (14.0%)	14 (28.0%)	21 (21.0%)	.086
	No	43 (86.0%)	36 (72.0%)	79 (79.0%)	

TABLE-III

Stratified analysis of efficacy by demographic and clinical factors

Variable		Group	Group-A (Count, %)	Group-B (Count, %)	Total (Count, %)	P-Value
Age	18–30	Yes	13 (50.0%)	8 (27.6%)	21 (38.2%)	0.088
		No	13 (50.0%)	21 (72.4%)	34 (61.8%)	
	31–40	Yes	11 (45.8%)	4 (19.0%)	15 (33.3%)	0.057
		No	13 (54.2%)	17 (81.0%)	30 (66.7%)	
Gender	Male	Yes	15 (46.9%)	8 (30.8%)	23 (39.7%)	0.212
		No	17 (53.1%)	18 (69.2%)	35 (60.3%)	
	Female	Yes	9 (50.0%)	4 (16.7%)	13 (31.0%)	0.021
		No	9 (50.0%)	20 (83.3%)	29 (69.0%)	
Grade at baseline	I	Yes	10 (43.5%)	4 (18.2%)	14 (31.1%)	0.067
		No	13 (56.5%)	18 (81.8%)	31 (68.9%)	
	II	Yes	9 (47.4%)	5 (27.8%)	14 (37.8%)	0.219
		No	10 (52.6%)	13 (72.2%)	23 (62.2%)	
	III	Yes	5 (62.5%)	3 (30.0%)	8 (44.4%)	0.168
		No	3 (37.5%)	7 (70.0%)	10 (55.6%)	
Complications	No	Yes	22 (51.2%)	8 (22.2%)	30 (38.0%)	0.008
		No	21 (48.8%)	28 (77.8%)	49 (62.0%)	
	Yes	Yes	2 (28.6%)	4 (28.6%)	6 (28.6%)	1.000
		No	5 (71.4%)	10 (71.4%)	15 (71.4%)	

A similar trend was observed in the 31–40 years age group (efficacy 45.8% vs. 19.0%, p = 0.057), suggesting a potentially age-independent superiority of bevacizumab. Gender analysis revealed no significant difference in male response rates between groups (46.9% for bevacizumab vs. 30.8% for diathermi; p = 0.212).

Our findings are consistent with Adnane et al., who reported 60% vessel regression using bevacizumab, compared to 35% with diathermy.[10] Elbaz et al. observed enhanced efficacy when both modalities were combined in pediatric patients, with 89% neovascular regression.[11] Although combination therapy may offer improved outcomes, our data confirm that bevacizumab alone remains highly effective and feasible in resource limited settings. Previous animal and clinical studies have shown the role of VEGF in corneal neovessels(NV) and the effectiveness of anti-VEGF agents such as bevacizumab, ranibizumab, and aflibercept.[14-15] However, their impact may be limited in cases involving chronic or deep stromal vessels. Hsu et al. emphasized that anti-VEGF drugs are more effective in early or superficial corneal neovessels (NV), with declining efficacy in mature neovessels.[8] Eski et al. found comparable regression in experimental models across bevacizumab, ranibizumab, and aflibercept groups, though aflibercept had a slight edge.[14] Bilgin further confirmed bevacizumab's superiority over interferon alpha-2a in corneal neovessels (NV) reduction.[16] Nonetheless, in our human study, bevacizumab alone yielded significantly lower efficacy and more complications.

Histopathological studies by Ozdemir et al. demonstrated reduced inflammation and fibroblast activity with bevacizumab treatment, particularly via subconjunctival delivery.[15] Additionally, Wu et al. and Feizi et al. emphasized the role of mechanical vessel closure methods like fine needle Diathermy in achieving sustained corneal neovessels(NV) control, especially when combined with pharmacologic anti-angiogenesis.[13,17] The future may lie in multimodal therapy, incorporating anti-VEGF, gene therapy, and Diathermy or photocoagulation as individualized treatment options.[18]

This study strengthens the evidence supporting bevacizumab as a more effective, safe, and economical treatment modality for superficial corneal neovessles (NV), especially in settings where access to biologics like bevacizumab is limited. Furthermore, better outcomes with bevacizumab, warranting further subgroup investigations. Limitations include the short follow-up duration (4 weeks), which may not capture long-term recurrence, and the focus on superficial neovessels only.

CONCLUSION

This trial demonstrated that bevacizumab injection is significantly more effective than Diathermy in achieving regression of superficial corneal neovascularization. Bevacizumab achieved a higher rate of vascular regression with fewer complications, making it a more effective and practical choice, especially in resource limited settings. Given the potential for recurrence and varied individual response, future studies should explore the long-term outcomes of combination therapy and evaluate responses based on vessel depth and chronicity. These findings can guide ophthalmologists in selecting cost-effective, targeted management strategies for corneal neo vessels.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORSHIP AND CONTRIBUTION DECLARATION	
1	**Sidra Ahsan Shah:** Data collection.
2	**Sidrah Latif:** Concept, design.
3	**Iqra Shamim Ahmed:** Drafting.
4	**Fauzan Ayub:** Literature review.
5	**Muhammad Qasim Yazar:** Data analysis.