Biomedical and Biopharmaceutical Research
Abbreviation: Biomed. Biopharm. Res.
Volume: 22: Issue: 02 |Year: 2025
Page Number: 170-177

STUDY OF CLINICAL OUTCOMES OF INTRA-OPERATIVE ANTI-VEGF AGENT (BEVACIZUMAB) INJECTION GIVEN IN PATIENTS WITH NONPROLIFERATIVE DIABETIC RETINOPATHY DURING PHACOEMULSIFICATION SURGERY

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Article Received:21-02-2025

Article Accepted:28-03-2025

Abstract

Introduction: Diabetes is a growing worldwide epidemic that affected 463 Million individuals globally in 2019 and is projected to reach 700 million individuals by 2045. It has been estimated that 27% of patients with diabetes have evidence of diabetic retinopathy (DR).It is well established that after cataract surgery, patients with preexisting diabetic retinopathy (DR) have a significant risk for progression of DR, diabetic maculopathy, and anterior segment neovascularization.
A considerable proportion, ranging from 3.2% to 55% of individuals with diabetes, experience PCME after cataract surgery.
Aims and Objectives: Study of clinical outcomes of Intraoperative Anti-VEGF agent (Bevacizumab) injection given in patients with diabetic retinopathy during Phacoemulsification surgery.
Methodology: This prospective interventional study was conducted in the Department of Ophthalmology, Muzaffarnagar Medical College and Hospital, Begrajpur, in patients with Non Proliferative Diabetic Retinopathy & without Diabetic Macular Edema having cataract, undergoing Phacoemulsification. All the recruited patients were randomly divided into two groups-
Group A (with Intraoperative Anti VEGF Injection (Bevacizumab) and Group B (without Intraoperative Anti VEGF Injection (Control Group). The comparable parameters were pre and postoperative Best Corrected Visual Acuity and Central Foveal Thickness.
Results: The study found an occurrence of Diabetic macular edema in 8% of patients who had undergone cataract surgery without intraoperative intravitreal bevacizumab whereas no macular edema was noted in patients who had undergone cataract surgery along with intraoperative intravitreal bevacizumab. Majority of patients were in the age group of 55-65 years of age.
Conclusion: The findings indicate that intra-operative bevacizumab significantly improves postoperative best-corrected visual acuity (BCVA) and stabilizes central foveal thickness (CFT) over time compared to the control group. Patients receiving bevacizumab demonstrated better visual recovery and reduced fluctuations in macular thickness, suggesting a potential protective effect against postoperative diabetic macular edema.

Keywords: Anti VEGF, Bevacizumab, Best Corrected Visual Acuity, Central Foveal Thickness.

INTRODUCTION

Diabetes is a growing worldwide epidemic that affected 463 Million individuals globally in 2019 and is projected to reach 700 million individuals by 2045.[1,2] In 2021, approximately 537 million individuals globally were reported to have diabetes, with many unaware of their condition(Pradeepa & Mohan, 2024).[3]
Diabetic patients are more likely to develop cataracts than those without diabetes. It is believed that 27% of diabetics have diabetic retinopathy (DR). It is estimated that 20% of cataract surgeries in the Western world are performed on diabetic patients. Diabetes is far more common in developing countries, where a large number of patients undergoing

cataract surgery have the condition. It is well established that after cataract surgery, patients with preexisting diabetic retinopathy (DR) have a significant risk for progression of DR, diabetic maculopathy, and anterior segment neovascularization.[4,5,6]

DR is a common microvascular complication of diabetes, significantly contributing to increased morbidity and mortality, and imposing a financial strain on healthcare systems.[3] DR results from the development of weak blood vessels in the retina, leading to blood leakage and potential blindness in individuals aged 25–65.[7] The progression of DR is closely linked to factors such as poor glycemic control, duration of diabetes, and systemic risk factors like hypertension and dyslipidemia.[8].Many ocular and systemic conditions are noted to increase the risk of PCME, one of the major co-morbidities being diabetes [9] .Diabetes mellitus presents an elevated susceptibility to cataracts and exacerbates their advancement in affected individuals [10]. Considering the inevitability of cataract surgery in such instances, various parameters, such as the length, intensity, type of diabetes, rigidity of the lens, and HbA1C levels, all contribute to the risk assessment [11]. A considerable proportion, ranging from 3.2% to 55% of individuals with diabetes, experience PCME after cataract surgery [12,13] This occurrence can be attributed to poor blood-aqueous barrier function within this patient group [14]

Phacoemulsification is one of the most common surgical procedures which is being performed in diabetic patients through the world.[15] It has been shown that even an uncomplicated phacoemulsification may lead to macular edema in non-diabetic patients and those who are not predisposed to this complication.[16] In diabetic eyes, however, the increased level of vascular endothelial growth factor (VEGF) in aqueous humor has been observed at 1 day after surgery.[17]

Given the importance of angiogenic factors like as VEGF in the progression of diabetic retinopathy, the development of anti-VEGF medicines for both prevention and management of diabetic retinopathy after or during cataract surgery has sparked great interest.

Recently anti-VEGF agents, particularly Bevacizumab, play a crucial role in managing diabetic retinopathy by targeting the vascular endothelial growth factor (VEGF) pathway, which is pivotal in the disease's pathogenesis.[18] Bevacizumab, an anti-VEGF agent, binds to VEGF, a protein that promotes the growth of abnormal blood vessels in the retina and thus inhibits its activity. This effect helps to prevent diabetic retinopathy by reducing neovascularization and vascular permeability.[18, 19]

In experimental models, Bevacizumab has been shown to decrease the expression of VEGF and its receptor Flk-1, as well as other signaling molecules like protein kinase C, which are involved in the pathological changes seen in diabetic retinopathy.[19]

MATERIALS AND METHODS

This prospective interventional study entitled **"STUDY OF CLINICAL OUTCOMES OF INTRA-OPERATIVE ANTI-VEGF AGENT (BEVACIZUMAB) INJECTION GIVEN IN PATIENTS WITH NONPROLIFERATIVE DIABETIC RETINOPATHY DURING PHACOEMULSIFICATION SURGERY"** was conducted after clearance from Board of Studies and Ethical committee in the Department of Ophthalmology, Muzaffarnagar Medical College and Hospital, Begrajpur, Muzaffarnagar, UP. during the period March 2023 to August 2024." The patients with Non Proliferative Diabetic Retinopathy & without Diabetic Macular Edema having cataract, undergoing Phacoemulsification were selected.

Examination of patient

A complete pre-operative and post-operative ocular examination was done.

a) Pre-operative examination consisted of the following:
   1. Determination of best corrected visual acuity (BCVA) by Snellen's chart.
   2. Determination of CFT on Macular OCT.
   3. Slit lamp examination of the anterior segment.
   4. Fundus examination by Indirect Ophthalmoscope or Slit Lamp Biomicroscopy using +90D lens.
   5. Keratometry was carried out using the Bausch & Lomb type Keratometer.
   6. IOL power calculation.

Other routine examinations which include determination of the:

   1. Intraocular pressure (IOP) by applanation tonometry.
   2. Patency of the nasolacrimal duct by syringing.
   3. Axial length using the A-scan,
   4. General examination."

All the recruited patients were randomly divided into two groups-

Group A (with Intraoperative Anti VEGF Injection (Bevacizumab) and Group B (without Intraoperative Anti VEGF Injection (Control Group).

5. Preoperative Blood glucose levels & HbA1c report.

All the patients were examined next day of surgery after removing the bandage & cleaning.

b) Post - operative examination at each follow up visit will include the following:
   1. Postoperative complete examination of Anterior Segment.

2. Determination of the best corrected visual acuity (BCVA).
3. Determination of Central Foveal Thickness on macular OCT.
4. Postoperative thorough fundus examination was done on each visit.

Follow up of the patients was done at one , four and twelve weeks after surgery.

COLD CHAIN MAINTAINANCE:

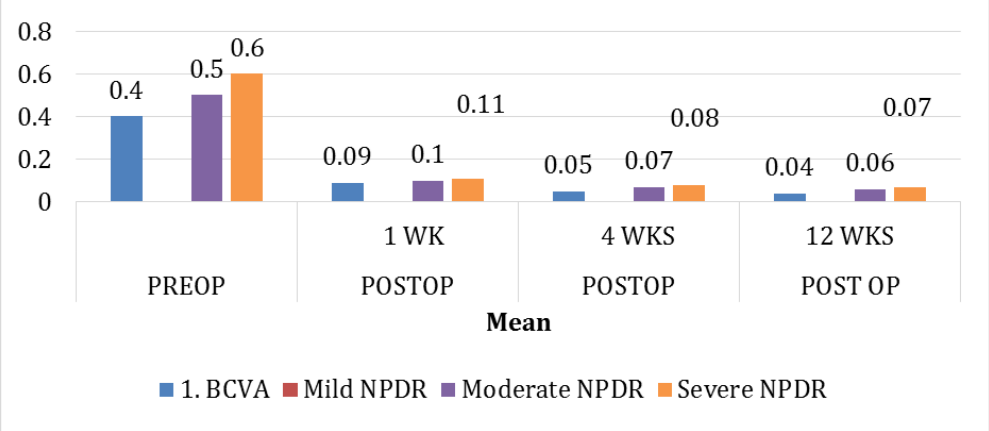
Appropriate measures were taken for cold chain maintainance during transportation of Avastin (Bevacizumab) injection and it was stored at a temperature of 2 to 8 degree celsius in the OT Refrigerator or in insulated box with ice packs.

RESULTS

The findings provided insights into the potential benefits and safety of bevacizumab during cataract surgery in diabetic patients, contributing to evidence-based improvements in ophthalmic care. Fifty patients of non proliferative diabetic retinopathy without diabetic macular edema were selected through randomization and distributed into two groups(A & B) of 25 patients each, where group A were given intravitreal bevacizumab intraoperatively during cataract surgery and group B was the control group.

Table 1: Best Corrected Visual Acuity (BCVA) in LogMAR in Group A patients pre and post surgery.

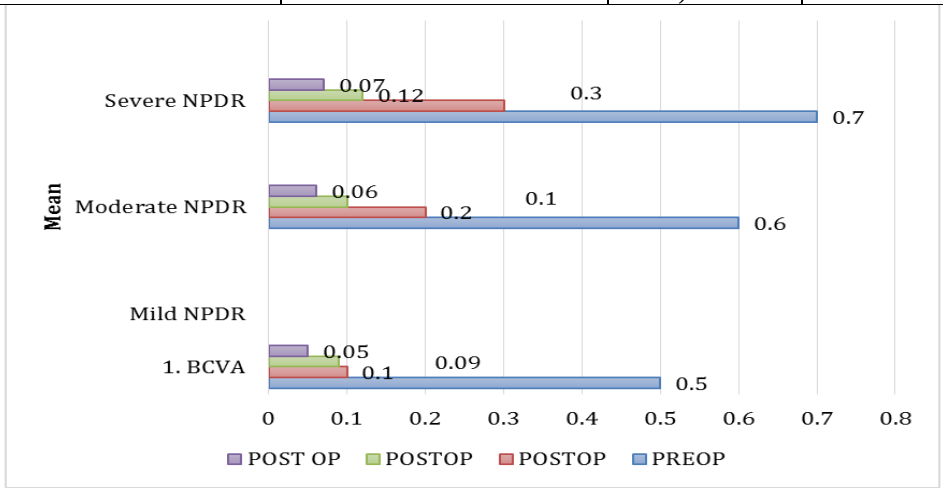
WITH Intraoperative Anti VEGF (Intravitreal Bevacizumab)	PREOP	POSTOP 1 WK	POSTOP 4 WKS	POST OP 12 WKS
1. BCVA Mild NPDR	0.4±0.3	0.09±0.02	0.05±0.07	0.04±0.03
Moderate NPDR	0.5±0.4	0.1±0.03	0.07±0.06	0.06±0.04
Severe NPDR	0.6±0.5	0.11±0.04	0.08±0.03	0.07±0.04
P-value	0.01		0.05 (preop with post op 4 week)	0.05 (preop with post op 12 week)



"Best Corrected Visual Acuity (BCVA) in group A subjects with intra-operative anti-VEGF (intravitreal bevacizumab) injection showed significant improvements in visual acuity over time. For mild non-proliferative diabetic retinopathy (NPDR), the preoperative BCVA was 0.4 ± 0.3, which decreased to 0.09 ± 0.02 at 1 week post-op, 0.05 ± 0.07 at 4 weeks post-op, and 0.04 ± 0.03 at 12 weeks post-op. For moderate NPDR, BCVA improved from 0.5 ± 0.4 preoperatively to 0.1 ± 0.03 at 1 week post-op, 0.07 ± 0.06 at 4 weeks, and 0.06 ± 0.04 at 12 weeks. Severe NPDR patients had a BCVA of 0.6 ± 0.5 preoperatively, which decreased to 0.11 ± 0.04 at 1 week post-op, 0.08 ± 0.03 at 4 weeks, and 0.07 ± 0.04 at 12 weeks. Statistically significant changes were observed when comparing preoperative values with post-operative values at 4 weeks ($p = 0.05$) and at 12 weeks ($p = 0.05$)."

Table 2: Best Corrected Visual Acuity (BCVA) in LogMAR in Group B patients pre and post surgery .

WITHOUT Intraoperative Anti VEGF (Intravitreal Bevacizumab)	PREOP	POSTOP 1 WK	POSTOP 4 WKS	POST OP 12 WKS
1. BCVA Mild NPDR	0.5±0.3	0.1±0.02	0.09±0.05	0.05±0.04
Moderate NPDR	0.6±0.4	0.2±0.03	0.10±0.07	0.06±0.06
Severe NPDR	0.7±0.6	0.3±0.05	0.12±0.08	0.07±0.07
p-value	0.01		0.05 (preop with post op 4 week)	0.05 (preop with post op 12 week)



Best Corrected Visual Acuity (BCVA)in group B subjects without intra-operative anti-VEGF (intravitreal bevacizumab) injection showed improvements in visual acuity over time, similar to the group with bevacizumab. For mild non-proliferative diabetic retinopathy (NPDR), the preoperative BCVA was 0.5 ± 0.3, which improved to 0.1 ± 0.02 at 1 week post-op, 0.09 ± 0.05 at 4 weeks post-op, and 0.05 ± 0.04 at 12 weeks post-op. For moderate NPDR, BCVA improved from 0.6 ± 0.4 preoperatively to 0.2 ± 0.03 at 1 week post-op, 0.10 ± 0.07 at 4 weeks, and 0.06 ± 0.06 at 12 weeks. In severe NPDR, BCVA improved from 0.7 ± 0.6 preoperatively to 0.3 ± 0.05 at 1 week post-op, 0.12 ± 0.08 at 4 weeks, and 0.07 ± 0.07 at 12 weeks. Statistically significant changes were noted when comparing preoperative values with post-operative values at 4 weeks (p = 0.05) and at 12 weeks (p = 0.05).

Table 3: Central Foveal Thickness(CFT) in Group A patients pre and post surgery .

WITH Intraoperative Anti VEGF (Intravitreal Bevacizumab)	PREOP	POSTOP 1 WK	POSTOP 4 WKS	POST OP 12 WKS
1. CFT Mild NPDR	260.7±36.6	255.3±29.6	248.3±29.6	244.3±29.6
Moderate NPDR	269.1±39.7	262.9±31.7	251.7±31.7	248.3±31.7
Severe NPDR	281.8±39.2	263.7±36.4	261.6±36.4	259.3±36.4
P-value	0.00		0.05 (preop with post op 4 week)	0.05 (preop with post op 12 week)

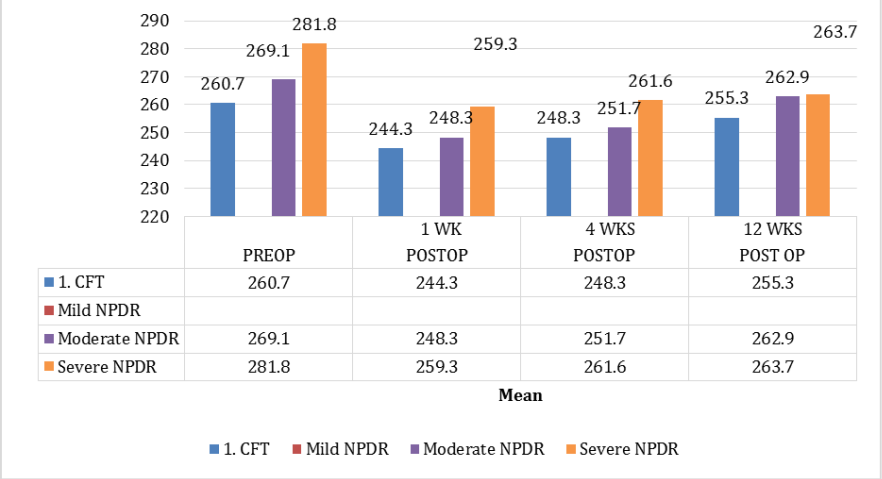
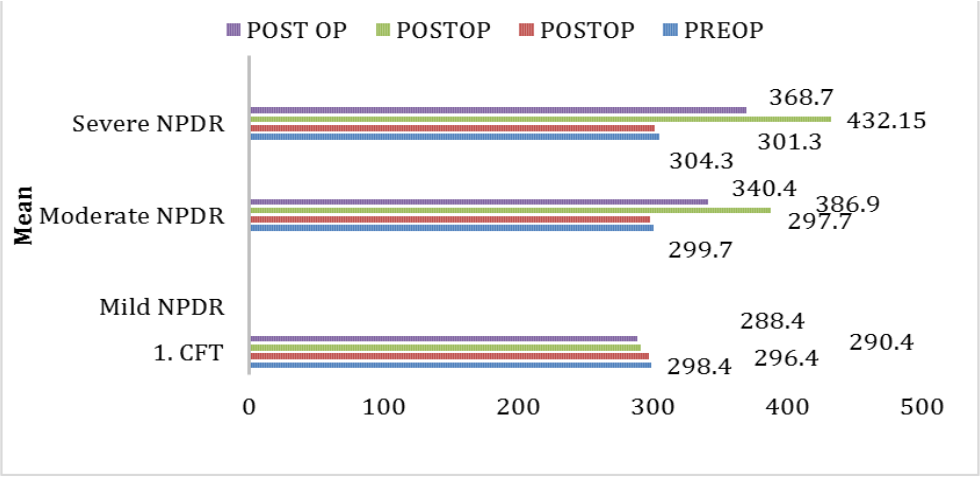


Table 11 presents the longitudinal changes in Central Foveal Thickness (CFT) among Group A patients who received intraoperative anti-VEGF therapy (Intravitreal Bevacizumab). The results indicate a progressive reduction in CFT across all severity levels of Non-Proliferative Diabetic Retinopathy (NPDR) over the 12-week postoperative period. In patients with mild NPDR, the mean CFT decreased from 260.7±36.6 µm preoperatively to 244.3±29.6 µm at 12 weeks postoperatively. Similarly, in moderate NPDR, CFT reduced from 269.1±39.7 µm preoperatively to 248.3±31.7 µm at 12 weeks. The most significant reduction was observed in severe NPDR, where CFT declined from 281.8±39.2 µm to 259.3±36.4 µm by the 12th week. Notably, the statistical analysis revealed a highly significant reduction in CFT (p = 0.00) across all NPDR subgroups, particularly evident at 4 weeks (p = 0.05) and 12 weeks (p = 0.05) postoperatively.

Table 4: Central Foveal Thickness(CFT) in Group B patients pre and post surgery:

WITHOUT Intraoperative Anti VEGF (Intravitreal Bevacizumab)	PREOP	POSTOP 1 WK	POSTOP 4 WKS	POST OP 12 WKS
1. CFT Mild NPDR	298.4±54.2	296.4±54.2	290.4±54.2	288.4±54.2
Moderate NPDR	299.7±53.7	297.7±53.7	386.9±73.2	340.4±57.9
Severe NPDR	304.3±59.4	301.3±59.4	432.15±69.6	368.7±59.5
P-value	0.00		0.01 (preop with post op 4 week)	0.01 (preop with post op 12 week)



The Central Foveal Thickness (CFT) in group B subjects without intra-operative anti-VEGF (intravitreal bevacizumab) injection showed varying results across time. For mild non-proliferative diabetic retinopathy (NPDR), the preoperative CFT was 298.4 ± 54.2 µm, which slightly decreased to 296.4 ± 54.2 µm at 1 week post-op, 290.4 ± 54.2 µm at 4 weeks post-op, and 288.4 ± 54.2 µm at 12 weeks post-op. For moderate NPDR, CFT decreased from 299.7 ± 53.7 µm

preoperatively to 297.7 ± 53.7 µm at 1 week post-op, but increased significantly to 386.9 ± 73.2 µm at 4 weeks, and then decreased to 340.4 ± 57.9 µm at 12 weeks. In severe NPDR, CFT decreased from 304.3 ± 59.4 µm preoperatively to 301.3 ± 59.4 µm at 1 week post-op, but increased to 432.15 ± 69.6 µm at 4 weeks, before improving to 368.7 ± 59.5 µm at 12 weeks. Statistically significant changes were observed when comparing preoperative values with post-operative values at 4 weeks ($p = 0.01$) and at 12 weeks ($p = 0.01$).

DISCUSSION

The research assessed the clinical results of intra-operative bevacizumab administration in individuals with non-proliferative diabetic retinopathy having phacoemulsification surgery. Fifty patients devoid of diabetic macular oedema were chosen using a randomised controlled experiment. The findings elucidated the prospective advantages and safety of bevacizumab in cataract surgery for diabetic patients, enhancing evidence-based advancements in ocular treatment.

In our study, postoperative BCVA improved significantly over time in both groups, with a more pronounced improvement in patients who received intra-operative bevacizumab (IVB). For mild non-proliferative diabetic retinopathy (NPDR), the mean BCVA in Group A improved from 0.4 ± 0.3 preoperatively to 0.04 ± 0.03 at 12 weeks postoperatively, while in Group B, BCVA improved from 0.5 ± 0.3 to 0.05 ± 0.04 over the same period. Statistically significant improvements were observed at 4 weeks ($p = 0.05$) and 12 weeks ($p = 0.05$) in both groups. These results suggest that IVB may enhance visual recovery following cataract surgery in diabetic patients. Our findings align with those of Takamura et al. (2009), who reported that BCVA improved significantly in both IVB-treated and non-IVB-treated groups, but the IVB group demonstrated greater visual gains by three months postoperatively.[20] Similarly, Wu et al. (2022) found that patients receiving IVB at the time of cataract surgery had superior BCVA outcomes compared to those who underwent cataract surgery alone, particularly at one and three months postoperatively.[21] Conversely, Salehi et al. (2012) observed that although IVB-treated patients showed an early improvement in BCVA, this benefit was not sustained at six months postoperatively, suggesting that IVB may provide short-term benefits but not long-term advantages in preventing visual decline.[14] This contrasts with our findings, where BCVA gains remained statistically significant at 12 weeks, indicating a sustained benefit of IVB in our cohort. Additionally, Zhao et al. (2019) conducted a meta-analysis comparing BCVA outcomes in IVB-treated and non-IVB-treated diabetic patients undergoing cataract surgery.[23] Their study found that BCVA improved in both groups, but the IVB group demonstrated a statistically significant advantage at one and three months, whereas the difference was not significant at six months. These findings highlight the potential role of IVB in improving early postoperative visual recovery in diabetic patients undergoing cataract surgery. While the long-term benefits of IVB remain debatable, our study suggests that IVB contributes to more rapid BCVA improvement postoperatively, particularly in the early recovery phase. Further long-term studies are needed to assess whether IVB provides sustained visual benefits beyond the 12-week period.

In our study, In Group A CFT decreased progressively over 12 weeks, with the most notable reduction in severe NPDR (281.8±39.2 µm to 259.3±36.4 µm). Statistical analysis confirmed a significant decline ($p = 0.00$), with notable reductions at 4 and 12 weeks ($p = 0.05$). In Group B (without IVB), CFT initially decreased but later increased significantly, particularly in moderate and severe NPDR, with a rise from 299.7 ± 53.7 µm to 386.9 ± 73.2 µm at 4 weeks and from 304.3 ± 59.4 µm to 432.15 ± 69.6 µm at 4 weeks. Statistically significant changes were observed at 4 weeks ($p = 0.01$) and 12 weeks ($p = 0.01$), indicating that IVB had a stabilizing effect on macular thickness.

Our results are consistent with Khodabandeh et al. (2018), who reported that CFT significantly decreased in the IVB group at 1 and 3 months postoperatively, whereas it significantly increased in the control group.[22] Similarly, Takamura et al. (2009) found that IVB effectively prevented an increase in macular thickness after cataract surgery, reinforcing the role of IVB in stabilizing postoperative macular edema.[20] However, some studies reported varying outcomes. Zhao et al. (2019) found that while IVB provided initial stabilization of CFT, long-term differences in macular thickness were not significant between IVB and non-IVB groups after 6 months.[23] Similarly, Salehi et al. (2012) observed that while IVB prevented early macular thickening, its effect diminished over time, suggesting the need for additional interventions such as laser photocoagulation.[24] These findings suggest that IVB effectively prevents early postoperative increases in macular thickness in diabetic patients undergoing cataract surgery. However, its long-term benefits remain uncertain, necessitating further research to determine the optimal treatment strategy for sustained macular stabilization.

The progression of diabetic macular edema resulting in poor postoperative visual recovery may make cataract surgery in diabetics questionable. To make results predictable & better, good glycemic control, prior laser or when not possible prior or simultaneous Anti-Vegf may assure good visual recovery.

CONCLUSION

This study evaluated the clinical outcomes of intra-operative bevacizumab injection in patients with non-proliferative diabetic retinopathy undergoing phacoemulsification. The findings indicate that intra-operative bevacizumab significantly improves postoperative best-corrected visual acuity (BCVA) and stabilizes central foveal thickness (CFT) over time compared to the control group. Patients receiving bevacizumab demonstrated better visual recovery and reduced fluctuations in macular thickness, suggesting a potential protective effect against postoperative diabetic macular edema. Despite comparable systemic parameters between the groups, significant differences in intraocular pressure (IOP) and systolic blood pressure (BP) were noted. Overall, intra-operative bevacizumab appears to be a safe and effective

adjunct in cataract surgery for diabetic patients, contributing to improved visual outcomes. Further large-scale studies are recommended to validate these findings and establish long-term benefits.

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