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Intravitreal injection with anti-vascular endothelial growth factor (anti-VEGF) in diabetic macular edema (DME) versus vitrectomy with internal limiting membrane (ILM) peeling with anti-VEGF as an adjuvant

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List of Abbreviations

BCVA	Best corrected visual acuity
CMT	Central macular thickness
CSME	Clinically significant macular edema
DM	Diabetes mellitus
DME	Diabetic macular edema
ELM	External limiting membrane
ERM	Epiretinal membrane
FFA	Fundus fluorescein angiography
GA	General anesthesia
ILM	Internal limiting membrane
IS	Inner segment
IVB	Intravitreal bevacizumab
LA	Local anesthesia
OCT	Optical coherence tomography
OS	Outer segment
PDR	Proliferative diabetic retinopathy
PPV	Pars plana vitrectomy
PVD	Posterior vitreous detachment

List of Abbreviations

PVR	Proliferative vitreoretinopathy
QALY	Quality-adjusted-life-year
VEGF	Vascular endothelial growth factor
£	British pound
$	US dollar

Summary

Background: Diabetic macular edema (DME) is a globally growing health problem and considered the most common form of sight-threatening retinopathy in diabetic patients. Although focal or grid laser photocoagulation was the mainstay of treatment, anti-vascular endothelial growth factor (VEGF) agents are now the standard of care. However, these therapies are expensive and some patients show inadequate response.

Purpose: To determine the effect of pars plana vitrectomy (PPV) for DME with preoperative intravitreal bevacizumab (IVB) compared to anti-VEGF only.

Methods: This was a retrospective study between 2011 and 2016 of 260 eyes of 130 patients who had vitrectomy for DME (*n*=130, PPV group, single surgeon AV) and patients who had IVI of anti-VEGF only (*n*=130, IVI group) were followed for at least 12 month. Charts were reviewed for best corrected visual acuity (BCVA), central macular thickness (CMT) measured by optical coherence tomography (OCT).

Results: The mean BCVA in LogMAR improved from 1.08 ± 0.64 at baseline to 0.71 ± 0.55 at 12-month in the PPV group ($P < 0.0001$) and in the IVI group, from baseline 0.49 ± 0.39 to 0.42 ± 0.36 at 12-month ($P < 0.029$). The mean CMT improved from 442 ± 200 μm at baseline to 348 ±149 μm at 12-month in the PPV group ($P < 0.001$). The mean CMT improved from 439 ± 166 μm at baseline to 368 ± 144 μm μm at 12-month in the IVI group

($P < 0.001$). Preoperative IVB, compared to without IVB, leads to reduction in intraoperative (6 cases vs. 10 cases) and postoperative bleeding (3 cases vs. 13 cases).

Conclusion: Vitrectomy with internal limiting membrane peeling is a cost-effective procedure which consistently results in central macular thickness reduction and leads to clinically significant improvement in BCVA comparable to serial intravitreal injection of anti-VEGF. Careful patient selection and meticulous preoperative OCT assessment are critical steps in the decision-making process. Preoperative intravitreal bevacizumab was associated with reduced intraocular bleeding intra- and postoperatively. The complication rate of vitrectomy is low and similar to what has been reported for this procedure. A large, comparative, prospective, randomized clinical trial of these two treatments is needed to determine which therapy is more effective.

1. Introduction

Diabetes mellitus (DM) is an increasingly prevalent disease causing a wide variety of systemic complications, often including ophthalmic conditions such as diabetic retinopathy. Diabetic retinopathy is one of the leading causes of vision loss in working-aged adults globally. From 1990 – 2010, diabetic retinopathy was ranked as the 5th most common cause of preventable blindness and 5th most common cause of moderate to severe visual impairment. In 2010, over one-third of an estimated 285 million people worldwide with diabetes have signs of diabetic retinopathy and one-third of these are afflicted with vision-threatening diabetic retinopathy, defined as severe non-proliferative diabetic retinopathy or proliferative diabetic retinopathy or the presence of diabetic macular edema (DME).[1,2]

Currently, available alternatives in the management of DME are metabolic control, macular photocoagulation, macular laser biostimulation, intravitreal administration of corticosteroids or anti-vascular endothelial growth factor (VEGF) agents, pars plana vitrectomy and various combinations of these methods. Early treatment diabetic retinopathy study (ETDRS) established the role of laser photocoagulation either focal/grid as a gold standard treatment for DME.[3] Also the use of anti-VEGF agents, either alone or in combination with laser, can reduce macular edema and prevent further visual deterioration.[4]

However, some patients with DME do not respond well to intravitreal anti-VEGF therapy and/or laser. In some patients, a mechanical component via vitreomacular traction or

tractional epiretinal membrane may contribute to the pathogenesis of DME. In such cases, performing vitrectomy and surgical relieving of mechanical traction has been suggested as an effective treatment for DME.[5]

Vitrectomy acts by releasing of mechanical macular traction with subsequent reduction in DME, improving retinal oxygenation, and removing inflammatory cytokines and VEGF adjacent to the retina.[6,7] Several studies evaluated the effects of vitrectomy with or without internal limiting membrane peeling in patients with non-tractional DME with variable results. Some authors reported postoperative anatomic and visual improvements [8,9] while others did not confirm visual acuity improvement.[10]

Bevacizumab (Avastin; Genentech, Inc, South San Francisco, California, USA) is a potent, cost-effective anti-VEGF agent.[11] Preoperative intravitreal bevacizumab has been reported to improve the dissection of the diabetic epiretinal membrane and decrease intra- and postoperative bleeding. Preoperative intravitreal bevacizumab is expected to be helpful especially in diabetic patients with active neovascularization and/or extensive or multiple layers of fibrovascular proliferation.[12,13]

1.1. Epidemiology

1.1.1. Global Prevalence of Diabetes Mellitus

World health organization (WHO) estimated that, globally, 422 million adults aged over 18 years were living with diabetes in 2014. The distribution of diabetic patients was estimated for the WHO South-East Asia and Western Pacific Regions (Table 1). The total number of diabetic people has steadily risen over the past few decades, due to population growth, increased population life expectancy, and increased prevalence of diabetes at each age. Globally, the number of people with diabetes has substantially increased between 1980 and 2014, rising from 108 million to 422 million (around four times) higher (Table 1).[14]

Table 1 Estimated prevalence and number of people with diabetes

WHO region Year	Prevalence (%)		Number (Millions)	
	1980	2014	1980	2014
Africa	3.1%	7.1%	4	25
The Americas	5%	8.3%	18	62
Middle East	5.9%	13.7%	6	43
Europe	5.3%	7.3%	33	64
South East Asia	4.1%	8.6%	17	96
Western Pacific	4.4%	8.4%	29	131
Total	4.7%	8.5%	108	422

1.1.2. Prevalence of Diabetes Mellitus in Germany

In 2016, the German Institute of Medical Documentation estimated the incidence of DM in Germany. Diabetes diagnosis was present in 6.4 million out of a total of 65.6 million insures in 2009 compared to 6.7 million out of 64.9 million insures in 2010. The total number of persons with type 2 diabetes was 4.6 million in 2009 compared to 4.7 million in 2010. The prevalence and incidence of type 2 diabetes rose steeply from age 50 to age 80. Among the persons above 80 years, every 4th suffers from diabetes mellitus. Peak incidence was at age 85, with annual 24 newly diagnosed cases of diabetes per 1000 persons. The study estimated that 5.8 million persons with type 2 diabetes are living in Germany.[15]

1.1.3. Epidemiology of Diabetic Retinopathy

Diabetic retinopathy is one of the leading causes of vision loss in the working population.[16] PDR is the most common vision-threatening disease, particularly among type 1 diabetic patients. However, DME is responsible for most of the visual loss experienced by patients with type 2 diabetes.[17] A pooled individual participant meta-analysis involving 35 studies conducted worldwide from 1980 to 2008, estimated global prevalence of any diabetic retinopathy and PDR among patients with diabetes to be 35.4 and 7.5 % respectively.[18]

Prevalence of any diabetic retinopathy and PDR was higher in type 1 diabetes, compared to type 2 diabetes (77.3 vs. 25.2 % for any diabetic retinopathy, 32.4 vs. 3.0 %

for PDR). The most clinically important risk factors for progressive vision loss include the duration of diabetes, hyperglycemia, and hypertension. Control of serum glucose levels and blood pressure are effective in preventing vision loss due to diabetic retinopathy. [18]

In the USA, the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) found that among patients with insulin-dependent diabetes with onset before the age of 30, who are presumed to have type 1 diabetes, the 4-year cumulative incidence of diabetic retinopathy was 59.0 %. At 10, 14 and 25 years, the cumulative incidence of diabetic retinopathy in the same cohort rose to 89.3 %, 95.9 %, and 97 %, respectively.[19]

1.1.4. Prevalence of DME

The prevalence of DME is progressively rising globally. DME represents fluid accumulation within the central retina, as a consequence of blood-retinal barrier failure. Clinically significant macular edema is the more severe spectrum of DME, is detected on clinical examination and defined as:

- Retinal thickening within 500 µm of the center of the macula.
- Exudates within 500 µm of the center of the macula, if associated with retinal thickening.
- Retinal thickening one-disc area (1500 µm) or larger, any part of which is within one disc diameter of the center of the macula.[20]

The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) cohort of patients with type 1 diabetes had the longest follow-up time of 25 years.[19] Interestingly, the cumulative incidence of DME and Clinically significant macular edema (CSME) in this cohort seemed to plateau at the 14-year mark (DME 26.1 %, CSME 17.0 %), with the latter 11 years with minimal additions to the 25-year cumulative incidence (DME 29 %, CSME 17 %). Available data on DME incidence in type 2 diabetes is limited and inconsistent [21,22] In newly diagnosed diabetic patients, the observed prevalence of DME was almost non-existent, with studies reporting it to be within 0 to 0.8 %.[23,24]

1.2. The Role of Vitrectomy in Diabetic Macular Edema

The vitreous is a transparent, gelatinous fluid that occupies about two-thirds of the volume of the eye. The vitreous is thought potentially to play a role in the development of DME through mechanical mechanisms leading to increased retinal vascular permeability.[6]

DME has multifactorial pathophysiology. Hyperglycemia, increased VEGF levels, inflammatory cytokines, altered blood-retinal barrier, taut thickened posterior hyaloid, thickened ILM and vitreomacular traction all play a role in the pathogenesis of DME. Multiple chemokines, cytokines, and multiple cellular elements are involved in the pathogenesis of DME. With the introduction of anti-VEGF agents, the treatment of DME has been refashioned, and the indication for laser therapy has been relatively underestimated. However, the response to anti-VEGF drugs in DME is variable, and many

patients with DME show incomplete resolution of fluid despite multiple intravitreal injections or in occasional circumstances, no response to anti-VEGF.[25]

The vitreomacular interface is an important contributor to DME development. vitreomacular interface can significantly affect the course and response to treatment of DME.[26,27] Reports suggested posterior vitreous detachment in diabetic patients render them less likely to develop macular edema and resorption of DME may occur after a spontaneous posterior vitreous detachment.[28]

Nasrallah and colleagues found patients without DME had a significantly higher rate posterior vitreous detachment than those with DME.[29] Lewis and colleagues reported that vitrectomy with induction of posterior vitreous detachment was effective in eyes with DME and a thick and taut posterior hyaloid membrane.[30] Subsequently, the role of vitrectomy in eyes without such a thick and taut hyaloid membrane, or even in eyes with posterior vitreous detachment became more evident.[31]

Furthermore, internal limiting membrane may play a role in the development of DME. [6,32,33] A hypothesis proposed by Mario supporting that the internal limiting membrane has selective permeability by which macular edema is sustained over time. The significant role of the internal limiting membrane in the pathogenesis of persistent diffuse diabetic macular edema might be explained by stressing the importance of colloid and protein accumulation and retention in the retinal interstitial space.[34]

Matsunaga and colleagues evaluated the internal limiting membrane histopathologically in diabetic eyes with macular edema as compared to non-diabetic controls. The thickness of the internal limiting membrane in the DM group was significantly increased (mean 4.8 ±1.6 μm) compared with nondiabetic macular hole group (mean 1.8 ± 0.6 μm).[35]

Therefore, vitrectomy with internal limiting membrane peeling may have a role in the treatment of cases with refractory DME without apparent traction.[6,10,26,30,33,36]

There are several theories support the theoretical value of vitrectomy for the treatment of DME, based on

(1) Vitrectomy removes anteroposterior vitreoretinal traction and tangential traction by the removal of contractile vitreous within the posterior hyaloid.[29,30]

(2) Vitrectomy removes numerous vasoactive and inflammatory factors, improves oxygenation of the macula by up to 10 times and increases macular blood flow in DME.[37,38]

(3) internal limiting membrane peeling during vitrectomy is thickened and pathologic tissue with altered function than internal limiting membrane removed in nondiabetic case.[35]

(4) During vitrectomy, intraoperative panretinal photocoagulation can reduce peripheral ischemia and thereby decrease levels of VEGF and other vascular permeability factors.[35]

1.3. The Role of Anti-VEGF in Diabetic Macular Edema

VEGF is a very important mediator responsible for blood-retinal barrier breakdown and has been demonstrated to increase vascular permeability in vivo.[39] Therefore, therapies with anti-VEGF properties represent an effective therapeutic modality.

Gandorfer measured VEGF-concentrations in premacular vitreous 1386.2 ± 2134 pg/ml, peripheral cortical vitreous 1169.7 ± 1840.3 pg/ml, and in mid-vitreous 1080.9 ± 1534.1 pg/ml.[6] Recently, results from trials have demonstrated that anti-VEGF ± laser photocoagulation provides a highly significant clinical outcome.[40] Therefore, anti-VEGF is considered to be the new mainstay in treating DME. Several effective anti-VEGF have been developed, including bevacizumab, ranibizumab, and aflibercept. [40,41]

Despite its promising efficacy in halting DME and improving the vision for the patients, intravitreal injection of anti-VEGF agents may be associated with devastating complications. Complications of intravitreal injection may include scleral weakness, lens injury, endophthalmitis, intraocular inflammation, rhegmatogenous retinal detachment and vitreous hemorrhage.[42]

1.3.1. Aflibercept

Aflibercept (Eylea), a recombinant fusion protein which binds with high-affinity to VEGF-A and placental growth factor. Intravitreal injection of aflibercept is approved for the treatment of DME in the United States and the European Union. The typical dose is 2

mg/0.05 ml. The efficacy and safety of intravitreal injection of aflibercept in DME have been demonstrated over 2 years in the VISTA and VIVID studies. Both trials showed that, after 52 and 100 weeks of treatment, when compared with macular laser photocoagulation, provides significantly greater improvements in both functional and anatomic outcomes.[43]

1.3.2. Ranibizumab

Ranibizumab (Lucentis) is a monoclonal antibody fragment, designed for intraocular use. It binds and inactivates all isoforms of VEGF-A. The intravitreal injection of ranibizumab is beneficial and relatively safe for the treatment of DME.[44] In several randomized clinical trials, ranibizumab had become a standard for treatment of DME. The usual dose of ranibizumab is 0.5 mg /0.05 ml. The RESTORE study was the first study to demonstrate that ranibizumab monotherapy provides a significantly superior benefit over laser in patients with visual impairment due to DME.[45]

1.3.3. Bevacizumab

Bevacizumab (Avastin) is a full-length, humanized, monoclonal antibody that binds to and inhibits all VEGF isoforms. In contrast to ranibizumab, bevacizumab is a complete antibody originally developed to target blood vessel growth in metastatic cancer deposits and is ‘off-label’.[46] It is very much cheaper than ranibizumab and aflibercept. The typical dose is 1.25 mg/ 0.05ml.

The debate over the use of bevacizumab versus ranibizumab and aflibercept was studied in a randomized controlled trial, comparing the effectiveness of aflibercept, bevacizumab, or ranibizumab, for DME. The study concluded that all 3 anti-VEGF groups showed visual acuity improvement from baseline to 2 years with a decreased number of injections in year 2 and among eyes with worse baseline visual acuity, aflibercept had superior 2-year visual acuity outcomes compared with bevacizumab.[47]

1.4. Cost Effectiveness

Cost-effectiveness analysis is a method for assessing the gains in health relative to the costs of different health interventions. Measuring cost-effectiveness by calculating the amount of money spent by a patient or insurer to prevent vision loss is deficient. Other important considerations including office visit costs, unrelated medical costs, and indirect costs, such as caregiver burden should be also considered.[48]

Ross and colleagues analyzed the cost-effectiveness of aflibercept, bevacizumab, and ranibizumab for DME treatment, and during the first year, the incremental cost-effectiveness ratios of aflibercept and ranibizumab compared with bevacizumab were $1 110 000 per quality-adjusted-life-year (QALY) and $1 730 000 per QALY, respectively. During 10 years, they were $349 000 per QALY and $603 000 per QALY.[49]

Nicod and colleagues analyzed the cost of vitrectomy for the treatment of vitreomacular interface abnormalities. All consumables, equipment, and staff salaries were included. The

average staff cost was 280.40 British pounds (£) [£184.90-£376.70]. The average cost of consumables was £534.60 [£406.55-£688.85] and of equipment £87.75 [£28.10-£139.15]. The average direct cost of vitrectomy in the theatre was £901.10 [£671.00-£1185.55]. Average out-of-surgery costs were estimated at £325.35, including nursing staff, extra consumables, and hospitalization costs.[50]

1.5. Optical Coherence Tomography (OCT)

OCT is a non-invasive, noncontact imaging technique that allows quantitative measurements of retinal thickness and volume. Furthermore, OCT provides images of the vitreous, retinal, and choroidal structure.[51]

In DME, OCT works well as a valuable diagnostic tool. DME usually starts in the outer retina (outer plexiform and Henle's fiber layer) secondary to loss of Müller cells then may progress to multiple central hyporeflective cysts. These cysts contribute to significant foveal thickening with loss of central foveal depression. Consequently, the main characters of DME in OCT include increased retinal thickness, intraretinal hypo reflective spaces, disintegration of the retinal layers, and loss of foveal contour. Sometimes neurosensory detachment, hard exudates, and hemorrhage may be present as small hyporeflective deposits with posterior shadowing. [52]

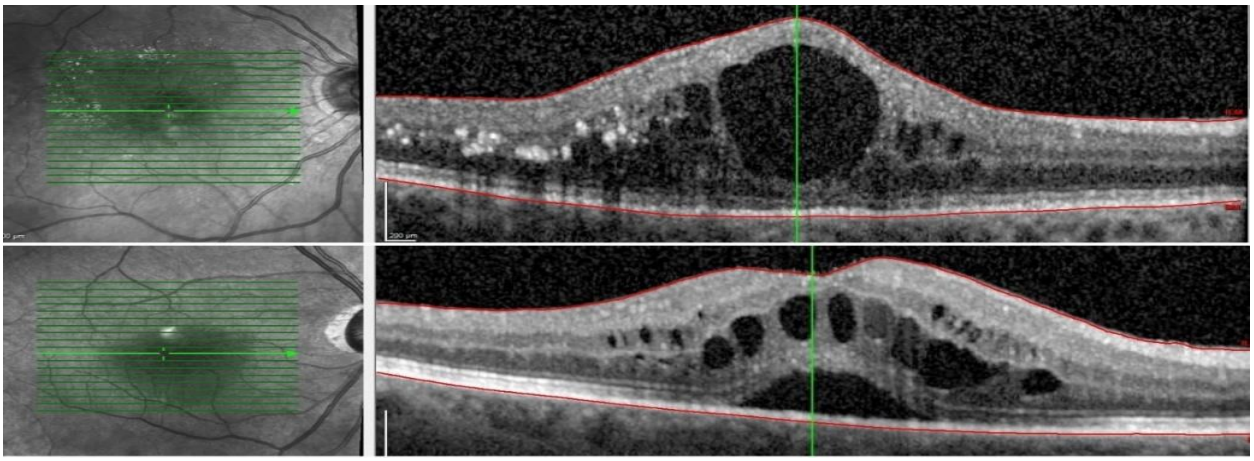

Figure 1 OCT scan showing CME with intact ELM and IS/OS junction with multiple hyperreflective foci (upper) shallow neurosensory detachment and multiple hyporeflective cystoid spaces (lower)

It is possible with spectral-domain OCT to precisely visualize the outer retinal layers and the integrity of the external limiting membrane and inner segment (IS)/ outer segment (OS) junction. Shin and colleagues reported the final visual outcome in DME is closely related to the status of the photoreceptor layer.[53] Therefore, careful assessment of the outer retinal layer structure should be a part of routine OCT evaluation in DME. OCT can uniquely visualize the vitreoretinal interface, allows valuable evaluation and assessment of traction exerted on the macula. The traction may be induced by incomplete posterior vitreous detachment or epiretinal membrane which at early stages cannot be visualized clinically, however, it can be only visualized using OCT. Careful assessment of the vitreomacular interface is an essential step in the evaluation of the macula in patients with diabetic

retinopathy. The detection of significant macular traction has a direct impact on decision making in the DME.[54]

Additionally, OCT can monitor the postoperative outcome and identify complications such as retinal detachment, epiretinal membrane, macular hole formation, and give us further important details about these complications (Figure 2). OCT represents the epiretinal membrane as a hyperreflective line lying on the retinal surface. In practice, the distinction between the epiretinal membrane and posterior vitreous detachment is required. This is usually made based on reflectivity. posterior vitreous detachment has a lower reflectivity and less consistent appearance than pre-retinal fibrosis. [52]

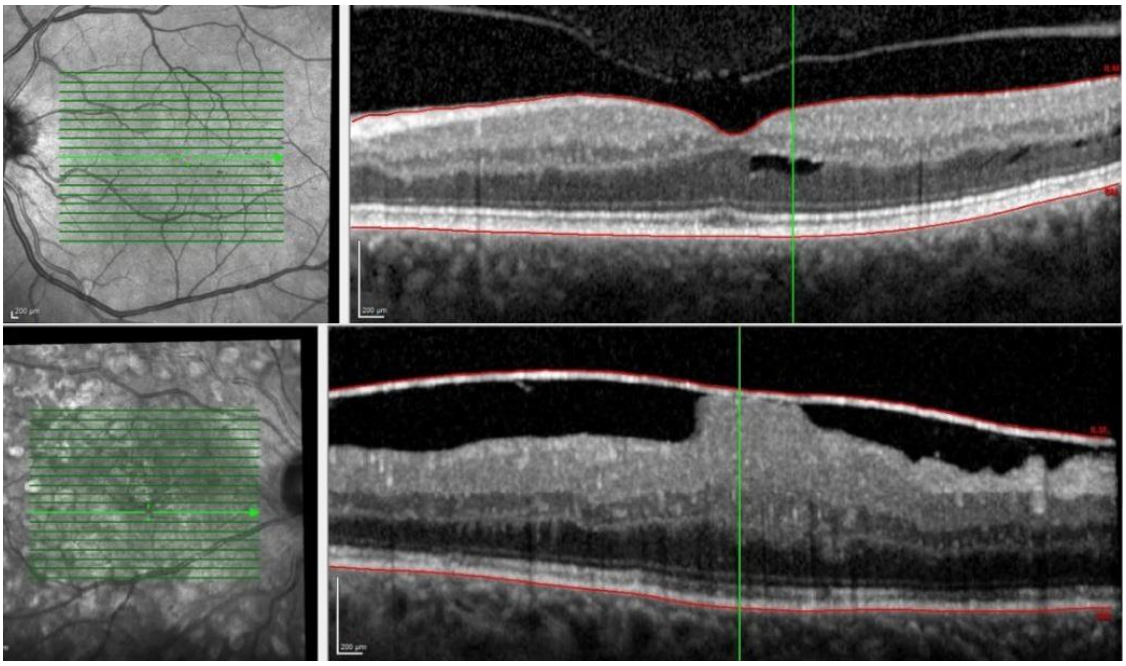

Figure 2 OCT scan showing complete posterior vitreous detachment with intraretinal hyporeflective foci (upper) vitreomacular traction syndrome with posterior hyaloid adherent to the fovea resulting in distortion of the foveal surface (lower)

2. Thesis Aim

This study aims to provide information on the following outcomes in eyes with DME.

1- To measure and compare best-corrected visual acuity (BCVA), central macular thickness (CMT), surgical complications in PPV group, and IVI group.

2- To identify subgroups in which there appears to be a benefit of vitrectomy and subgroups in which vitrectomy does not appear to be beneficial.

3- To assess the safety of vitrectomy vs. intravitreal injection in subjects with DME.

4- To correlate the visual outcome with central macular thickness.

3. Study Design

Retrospective, comparative analysis of patients with DME from 2011 until 2016 in Homburg/Saar.

3.1. Sample Size

A total of 260 eyes of 207 patients (130 eyes divided into 2 groups) met the inclusion and exclusion criteria.

All procedures were performed on the study eye only.

3.1.1. Inclusion Criteria

- *Subject selection*

1. Age 18 years. No pregnancy.
2. Diagnosis of diabetes mellitus (type 1 or type 2): Any one of the following was considered to be sufficient evidence that diabetes is present at the time of intervention:

- Current regular use of insulin for the treatment of diabetes.
- Current regular use of oral antihyperglycemic agents for the treatment of diabetes.
- Documented diabetes by WHO criteria: a random venous plasma glucose concentration ≥ 11.1 mmol/l or a fasting plasma glucose concentration ≥ 7.0 mmol/l (whole blood ≥ 6.1 mmol/l) or two-hour plasma glucose concentration

≥ 11.1 mmol/l two hours after 75g anhydrous glucose in an oral glucose tolerance test.

- *Study eye selection:*

- Vitrectomy is performed as a treatment for DME.
- Anti-VEGF performed as a treatment of DME.
- Definite retinal thickening due to DME based on clinical exam involving the center of the macula and central retinal thickness > 300 µm on OCT.
- Unresponsive to other DME therapies.

3.1.2. Exclusion Criteria

- Patients with DME treated with intravitreal injection of steroids (e.g. Ozurdex and Iluvien).
- Ocular conditions (e.g., foveal atrophy, optic atrophy, macular scar, AMD, CNV, CRVO, CRAO) that may affect the final visual outcome.
- History of PRP within 3 months before the intervention.

3.2. Intervention

Patients in PPV group had Pars plana vitrectomy (PPV group) ± preop avastin 1-4 days before surgery. The dose was 0.3 mg/ 0.05ml.

Patients in IVI group had intravitreal anti-VEGF injection (1.25 mg/0.05ml of Avastin, 0.5 mg/0.05 ml of Lucentis, 2 mg/0.05 ml of Eylea) for three monthly loading doses followed by injection as needed under pro re nata (PRN) protocol. All treated eyes had intravitreal injection with only one anti-VEFG agent except 2 cases were injected with both bevacizumab and ranibizumab.

3.3. Description of The Surgical Procedure

3.3.1. Pars Plana Vitrectomy

A standard pars plana vitrectomy was performed by a single surgeon (Prof. Dr. Viestenz), the procedure typically included:

- Anesthesia (general anesthesia (GA), Local anesthesia (LA)).
- Disinfection: 5% povidone-iodine solution placed on the globe and allowed to sit on the eye for at least 30-60 seconds. Wash out with BSS.
- Transconjunctival approach in 23 gauge PPV.
- 3 pars plana sclerotomies, 3-3.5mm for pseudophakic, 3.5-4.0 mm for phakic patients posterior to the surgical limbus.
- Core vitrectomy.
- Posterior vitrectomy: Removal of the vitreous gel with peeling of the posterior hyaloid, if a posterior vitreous detachment is not initially present, and removal of peripheral vitreous.

- Peeling off visually significant epiretinal membrane.
- Use of agents to improve visualization of membranes, such as brilliant blue G (MembraneBlue Dual, D.O.R.C. International).
- Removal of the internal limiting membrane using end-gripping 23g forceps.
- Examination and treatment of any peripheral breaks with endolaser or cryotherapy.
- Internal tamponading e.g. silicon oil, SF6, C3F8, or combination of gases.
- Closure of the sclerotomies with absorbable sutures if needed and re-approximation of the edges of the conjunctival incisions.
- Use of subconjunctival (dexamethasone + gentamycin) at the end of surgery.
- Optional additional procedures: Concurrent cataract extraction with intraocular lens implantation.

3.3.2. Intravitreal Injection Surgical Procedure

- Disinfection: 5% povidone-iodine solution placed on the globe and allowed to sit on the eye for at least 30-60 seconds.
- Topical proparacaine.
- 10% Betadine swab applied to inferotemporal quadrant and inferior cul-de-sac.
- Sterile eyelid speculum was placed.
- Location of injection was marked: 3-3.5 mm for pseudophakic, 3.5-4.0 mm for phakic patients.

- The patient was asked to look 90 degrees away from the injection site.
- The needle was inserted in the marked site in a smooth and single motion, aiming for the mid-vitreous cavity.
- As the needle moves out, the injection site was covered with a Q-tip.
- Finally, ensure optic nerve perfusion by asking the patient to count fingers (patient should be at least light perception).

3.4. Duration of Follow-up

All data were collected for one year after the date of the first intervention.

3.5. Main Outcomes

• BCVA.

• Central macular thickness measured on OCT (Spectralis, Heidelberg Engineering Inc., Germany).

• Surgical complications.

3.6. Testing Procedure

3.6.1. Historical Data

A history was extracted from available medical records. Data to be collected included: age, gender, diabetes duration and medications, HbA1c blood test and ocular diseases, surgeries, and treatment.

3.6.2. Baseline Data

3.6.2.1. Examination

Visual acuity testing, IOP measurement, slit lamp, fundus examination, and fundus fluorescein angiography (FFA, HRA, Heidelberg Engineering Inc., Germany). FFA can distinguish:

- PDR vs. NPDR.
- Areas of capillary dropout (macular ischemia & peripheral ischemia).
- Focal vs. diffuse leakage.

3.6.2.2. OCT parameters

1-Retinal thickness (RT): Central retinal thickness

- Normal: 170 ± 20 µm.
- Borderline: 190–230 µm.
- Edema: ≥230 µm.

2. Morphology:

- E1: simple thickening.
- E2: cystoid thickening.
- E3: neuroepithelial detachment.

3. Diffusion: Focal or diffuse (CSME criteria).

4. Epiretinal traction:

- T0: absence of epiretinal hyper-reflectivity.
- T1: the presence of a continuous line of flat hyper-reflectivity and adherent to the retina without significant retinal distortion.
- T2: the presence of a continuous line of hyper-reflectivity with multiple points of adhesion to the retina and with significant retinal distortion.
- T3: anterior-posterior traction with “gull wings” configuration.

3.6.3. Follow-up Data

At 1-, 3-, 6- and 12- month respectively and included:

1. Visual acuity testing.

2. Ocular examination of study eye, including slit lamp, IOP measurement, and dilated fundus examination.

3. Cataract assessment.

4. OCT of the macula.

5. Complications of surgery include:

- Risks of the vitrectomy procedure include retinal tear ± retinal detachment, cataract progression in phakic eyes, infection, and rebleeding.
- Risks of IVI procedure include retinal detachment, VH, endophthalmitis, and complicated cataract.

3.7. Statistical Analysis

For statistical analysis of the data, SPSS (SPSS release 17 for Windows, SPSS Inc., IBM, USA) was used.

Quantitative data were expressed as means ± standard deviation (mean ± SD). Parametric independent T-sample test (for comparisons of the means of two independent groups) and paired T-test (for comparisons of two related dependent data) were performed to compare VA, central macular thickness in baseline, and at 1-, 3-, 6- and 12-month respectively. Spearman´s test was used to determine the correlation between co-variables. $P < 0.05$ was considered statistically significant.

4. Results

4.1. Demographic & Historic Data

260 eyes of 207 patients who underwent PPV and IVI for DDME between 2011 and 2016 were analyzed. The mean age of the patients was 63 ± 15 years, 43% were females, and 220 (84.6%) had type 2 diabetes. Before surgery, prior treatment for DME had been administered in (75%) PPV group (either PRP (70%) or IVI (30%)), and (47%) in IVI group (table 2).

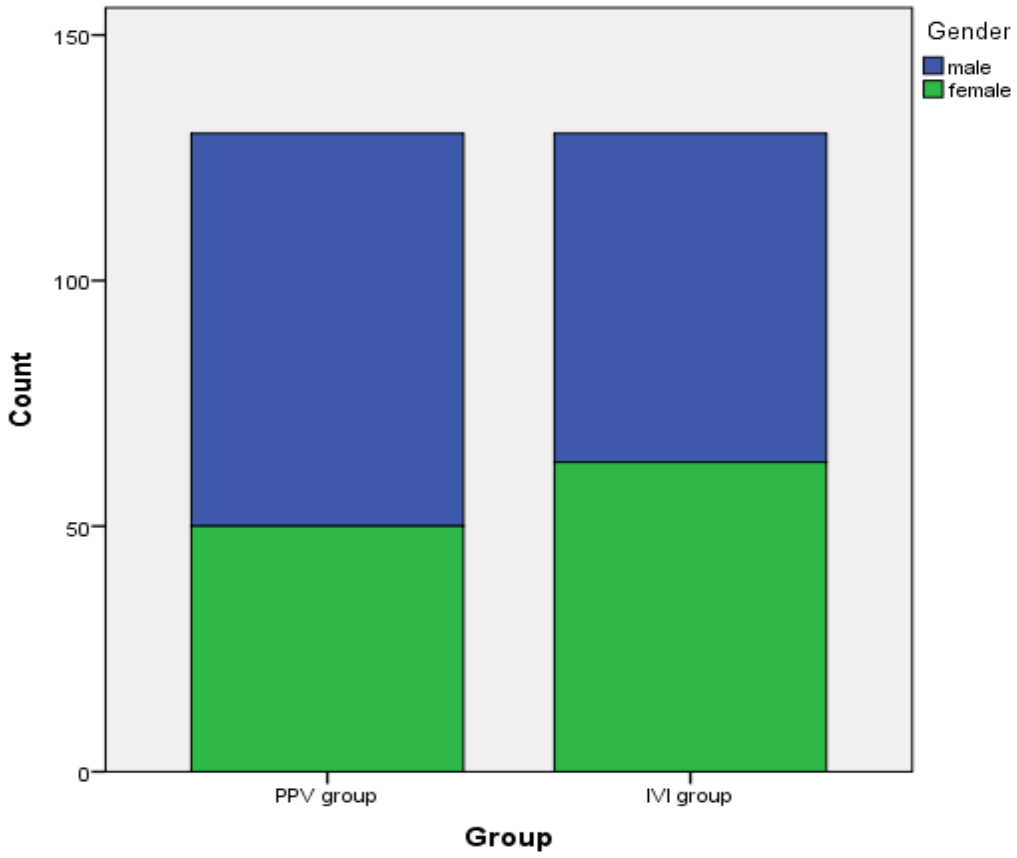

Figure 3 Gender distribution in PPV and IVI group

Table 2 Demographic data and patients characteristics

Characteristics	PPV group	IVI group
Number of patients	130	130
Gender (n): male/female	80/50	67/63
Mean age [years]	62 ± 14	65 ± 16
Lens-status (n): phakic/pseudophakic	75/55	68/62
Prior laser treatment (n)	91	56
Prior PPV	8	8
Prior IVI	40	0
No prior treatment	33	69
HbA1c level known	47/130	59/130
HbA1c level [%]	7.8 % ± 1.0	7.8 % ± 1.3
DM Type (n)		
-Type I/Type II	26/104	14/116
Mean duration of DM [years]	14 ± 8	13 ± 6

Results

Table 3 Baseline clinical & OCT and FFA examination

Characteristics	PPV group	IVI group
FFA:		
-Type of DR (n): NPDR/PDR	20/110	73/57
-Leakage	Diffuse	Diffuse
-Macular ischemia	13	0
OCT:		
-CMT, mean ± SD [µm]	442 ± 200	439 ±166
-VMT (n): T3/T2/T1/T0	8/23/42/57	3/5/1/121
-Morphology (n): E3/E2/E1	22/68/40	26/81/23
-ERM (n)	74	8
IOP, mean ± SD [mmHg]	14.3 ±4.3	13.0 ± 5.2
Rubeosis iridis (n)	13	0

Abbreviation: SD = standard deviation, CMT = central macular thickness, ERM = epiretinal membrane

The mean BCVA LogMAR improved from baseline 1.08 ± 0.64 to 0.71 ± 0.55 at 12-month in PPV group. In IVI group, the mean preoperative BCVA improved from baseline 0.49 ± 0.39 to 0.42 ± 0.36 at 12- month follow-up (table 4).

Results

Table 4 Visual acuity changes between both groups

BCVA, mean ± SD, LogMAR	PPV group	IVI group	*P*-value
Baseline	1.08 ± 0.64	0.49 ± 0.39	< 0.0001
1-month	1.35 ± 0.70	0.46 ± 0.37	< 0.0001
3-month	0.99 ± 0.64	0.44± 0.34	< 0.0001
6-month	0.76 ± 0.57	0.39 ±0.32	< 0.0001
12-month	0.71 ± 0.55	0.42 ± 0.36	< 0.0001
Delta baseline vs. 12-month	0.37	0.07	
P-value *	<0.0001	<0.029	

*BCVA at baseline vs. 12-month of the same group

Subgroup analysis

Table 5 BCVA in LogMAR units (mean, SD) in PPV group

Characteristic	Baseline	12-month
Phakic/pseudophakic	1.02 ± 0.63/1.17 ± 0.64	0.71 ± 0.59/0.73 ± 0.52
(n)	75/55	70/60
Prior PPV/ VFE	1.42 ± 0.51/1.06 ± 0.64	1.01 ± 0.63/0.68 ± 0.54
(n)	8/122	13/117
Ischemic maculopathy	0.87 ± 0.55	0.34 ± 0.26
(n)	12	13
Prior IVI/no prior IVI	0.84 ± 41/1.04 ± 0.64	0.66 ± 41/0.62 ± 0.52
(n)	20/110	20/110
VMT/no VMT	0.94 ± 0.58/1.18 ± 0.70	0.65 ± 0.54/0.72 ± 0.57
(n)	73/57	

Abbreviation: VFE = vitreous filled eye, VMT = vitreomacular traction

The mean central macular thickness followed a similar course in both groups, from baseline (442 ± 200 µm) to 12-month (348 ±149 µm) in PPV group ($p < 0.001$) compared to baseline (439 ± 166 µm) to 12-month (368 ± 144 µm) ($p < 0.001$) in IVI group (table 6).

Table 6 Central macular thickness changes compared to baseline

Characteristics	PPV group	IVI group	*P*-value
Baseline [µm]	442 ± 200	439 ± 166	0.10[a]
1-month [µm]	425 ± 172	420 ± 147	0.16[a]
3-month [µm]	389 ± 155	360 ± 149	0.79[a]
6-month [µm]	327 ± 127	364 ± 143	0.07[a]
12- month [µm]	348 ± 149	368 ± 144	0.91[a]
P-value*	<0.001[b]	<0.001[b]	
CRT-thinning over 12-month [µm]	94	71	

a=independent T-test, b=paired T-Test, *P*-value of baseline and 12-month of the same group

Table 7 OCT morphology in PPV group at baseline compared to 12-month follow-up

Characteristic (n)	Baseline	12 month	P-value
E1	(40) 315± 74	(48)308 ± 91	0.337
E2	(68) 467 ± 175	(78) 379 ± 154	0.0001
E3	(22) 650 ± 202	(4) 304 ±145	0.0001

Abbreviation: E1=simple thickening, E2=cystoid thickening, E3=neuroepithelial detachment.

4.2. Surgical Details

In PPV group, 92 patients had GA (70.8%), 23 gauge vitrectomy in 121 (93%) eyes, SF6 in 86 cases (66.2%), endolaser in 71 cases (54.6%). In IVI group, 88 ranibizumab, 30 bevacizumab, 7 aflibercept, and 2 cases were injected both bevacizumab and ranibizumab. Intraoperative iatrogenic opening or rupture of macular cysts was not observed in any patient, no iatrogenic retinal tear, and no lens touch (table 8).

Table 8 Surgical details in PPV group

Characteristics (n)	
Preoperative avastin	20
Anesthesia: GA/LA	92/38
Vitrectomy gauge: 20/23	9/121
Combined phacovitrectomy (*n*)	6
ILM stain: Brilliant blue/ICG	56/2
Tamponading agent	
Si Oil/ SF6/ SF6+C3F8/Air	16/86/15/13
Intra-operative bleeding (*n*):	
- Without IVB/With IVB	11/3
Endolaser (only) + cryocoagulation	(71)95

Abbreviation: Si Oil = Silicon oil, SF6 = sulfur hexafluoride, C3F8 = Perfluoropropane ICG = indocyanine green, GA = general anaesthesia, LA = local anaesthesia, IVB =intravitreal bevacizumab

Table 9 Surgical details in IVI group

Anti-VEGF agent	Number of eyes had IVI	Mean no. IVI ± SD
Ranibizumab	91	4.1 ± 2.0
Bevacizumab	30	5.8 ± 2.7
Aflibercept	7	6.0 ± 2.0
Ranibizumab followed by Bevacizumab	2	4.0 ± 1.4
Total	130	4.6 ± 2.3

4.3. Examination and Follow-up

Visual acuity:

Visual acuity was analyzed in terms of the percent of patients gaining three lines LogMAR. The last BCVA reading was compared to the recorded pretreatment BCVA.

At 1-month: In PPV group, increased VA by more than 3 lines (22.7%) was more evident than in IVI group (2.7%) (Figure 2).

At 3-month: In PPV group increased VA by more than 3 lines (12.7%) was more evident than in IVI group (3.1%) (Figure 3).

At 6-month: In PPV group, increased VA by more than 3 lines (8.2%) was more evident than in IVI group (3.1%) (Figure 4).

At 12-month: In PPV group increased VA by more than 3 lines (7.4%) was more evident than in IVI group (5.1%) (Figure 5).

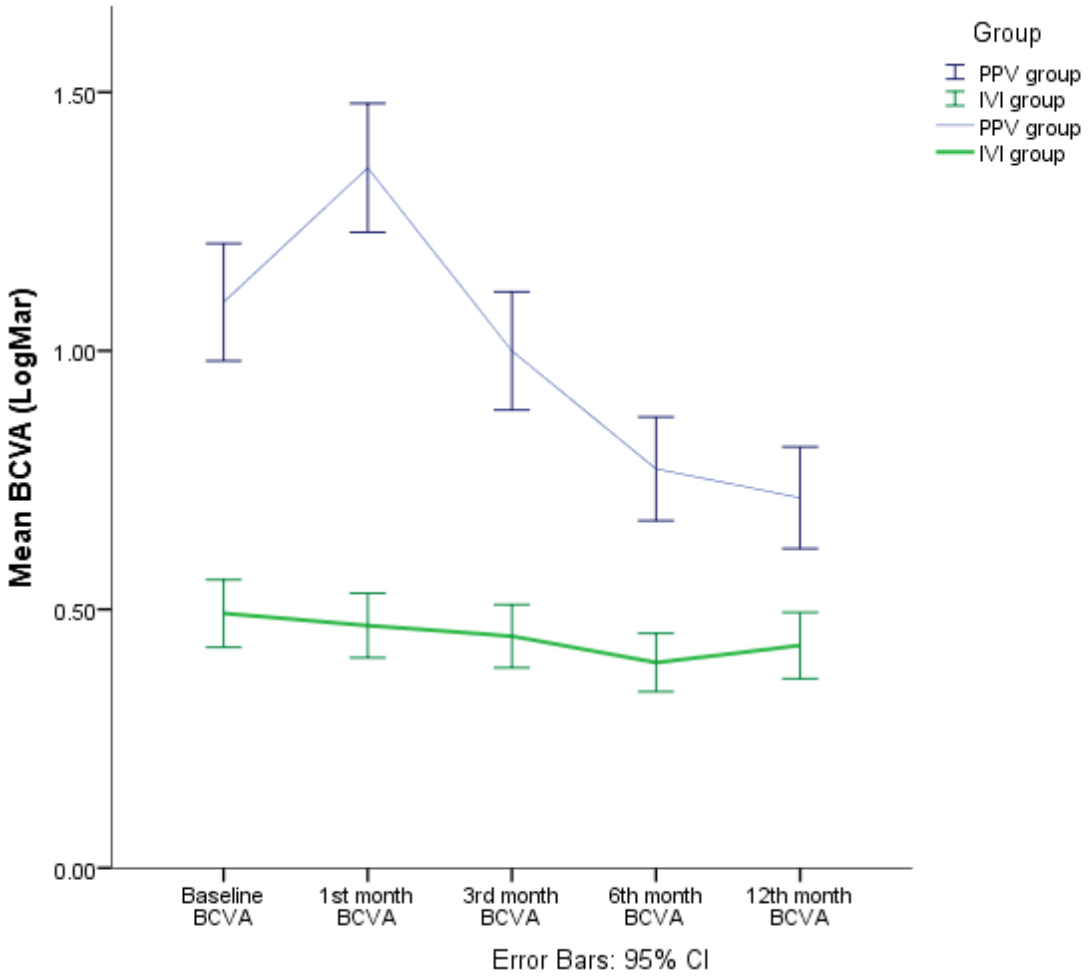

Figure 4 BCVA in PPV group vs. IVI group

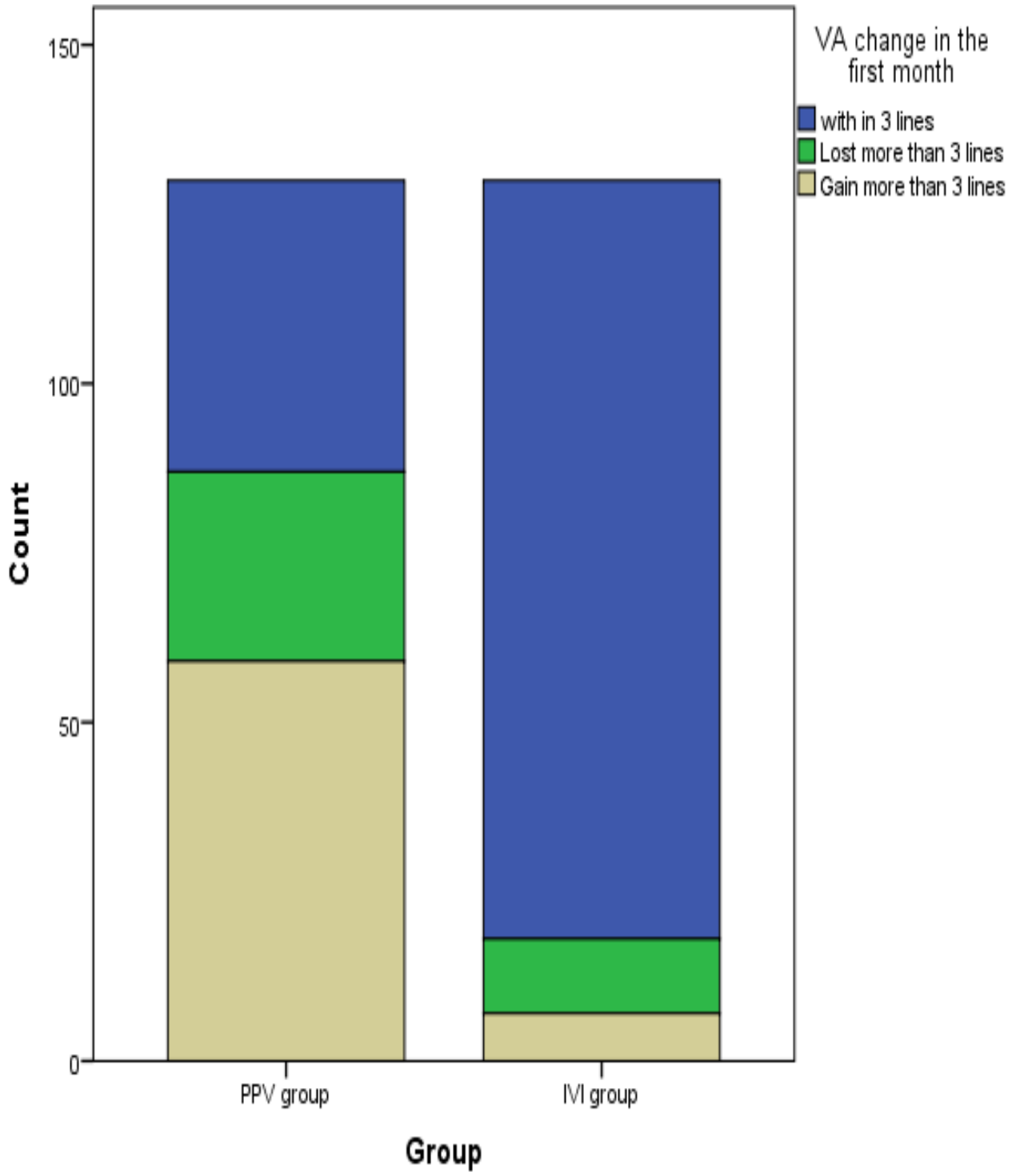

Figure 5 Follow up changes in visual acuity at the first month

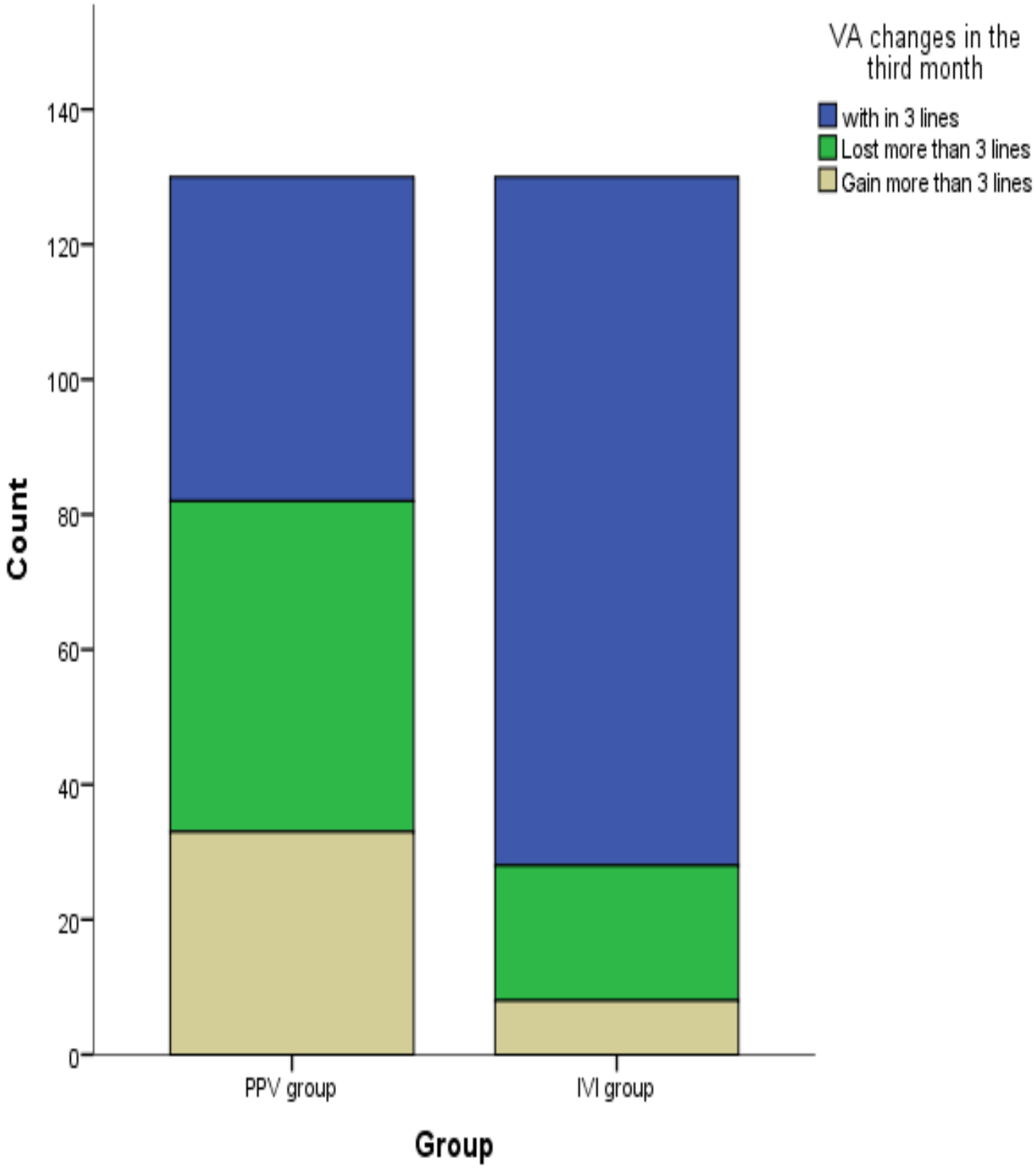

Figure 6 Follow up changes in visual acuity at the third month

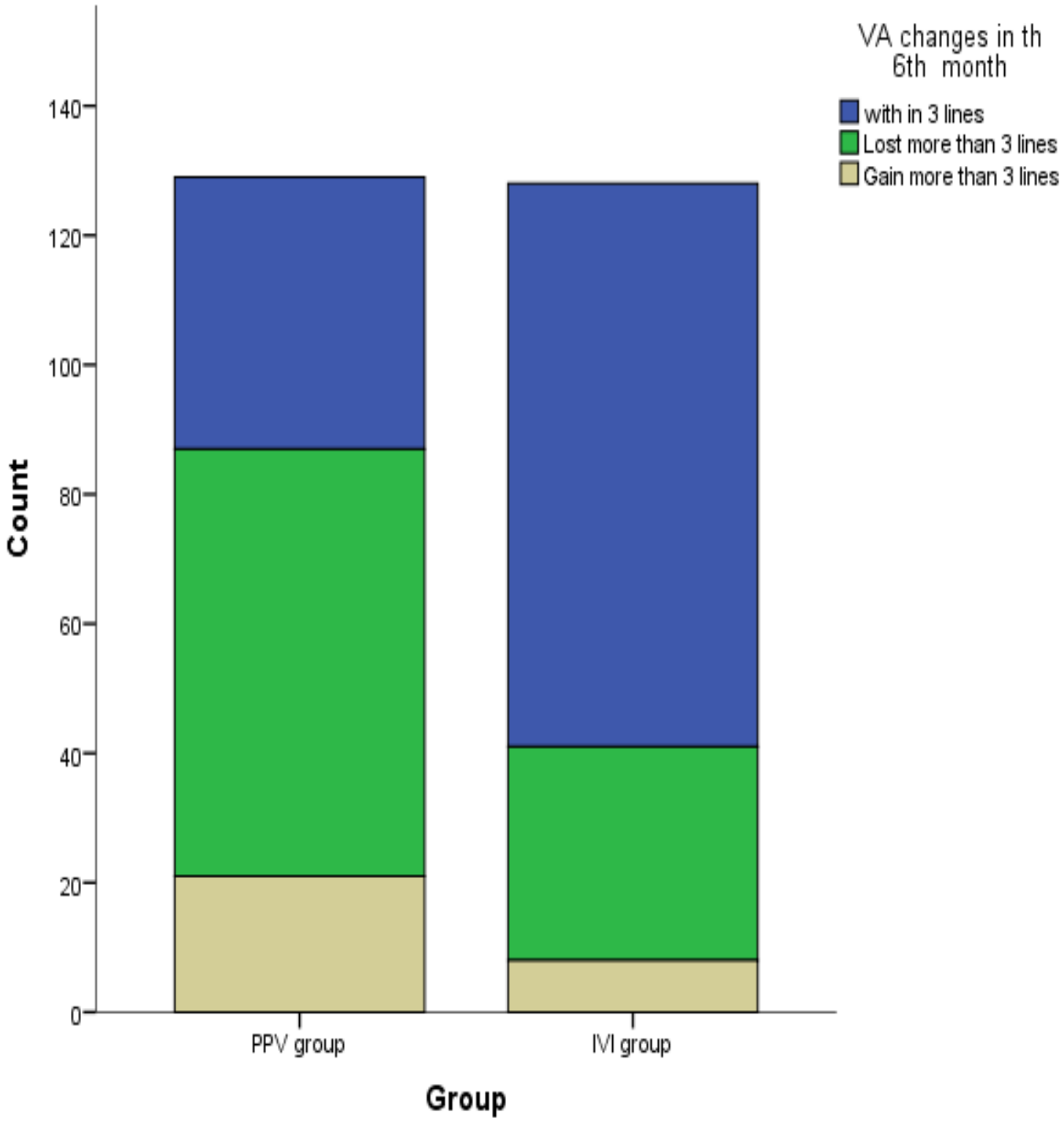

Figure 7 Follow up changes in visual acuity at the sixth month

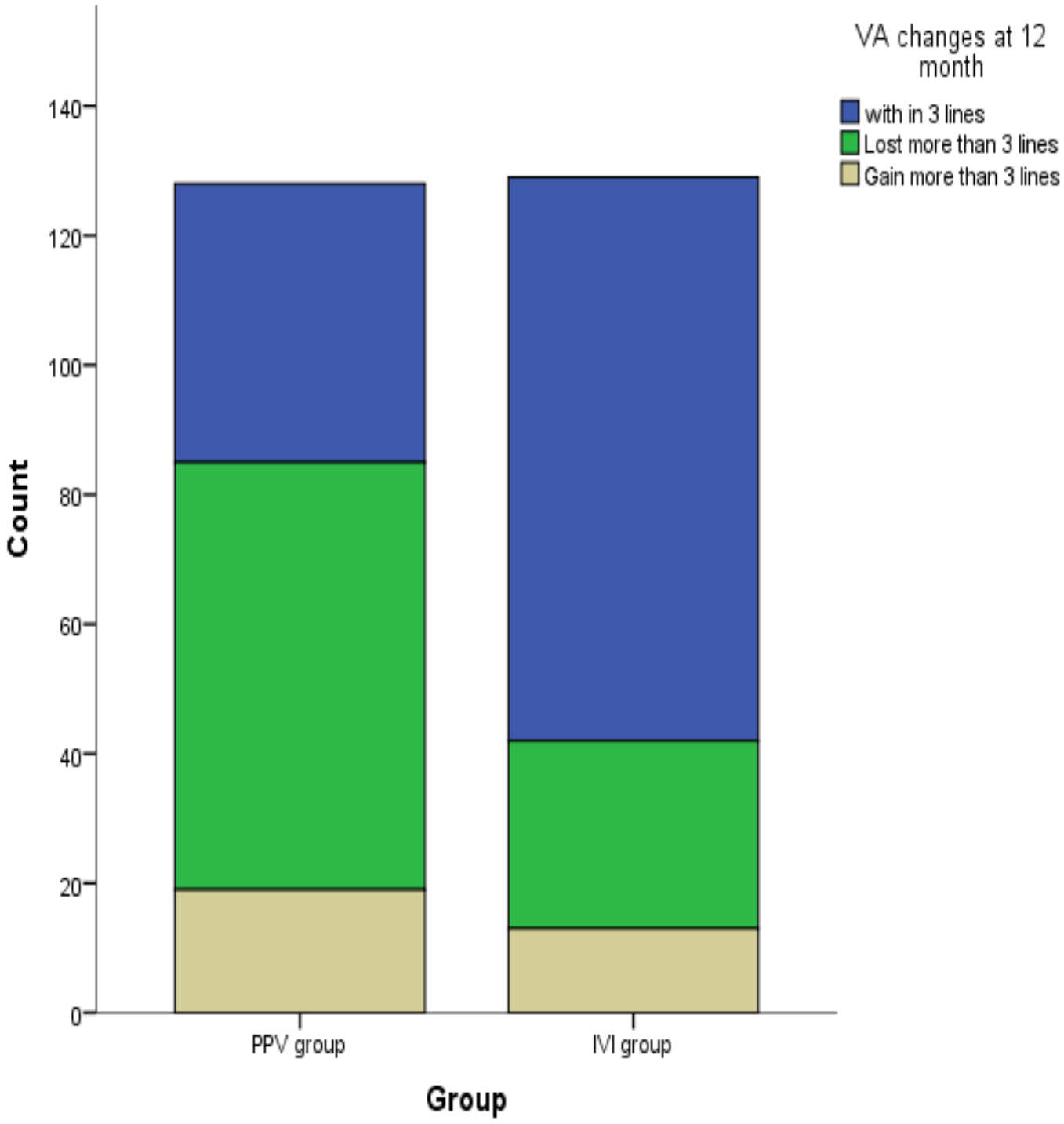

Figure 8 Follow up changes in visual acuity at the twelfth month

OCT:

The mean central macular thickness at the baseline was 442 ± 200 µm in PPV group compared to 439 ±166 µm in IVI group.

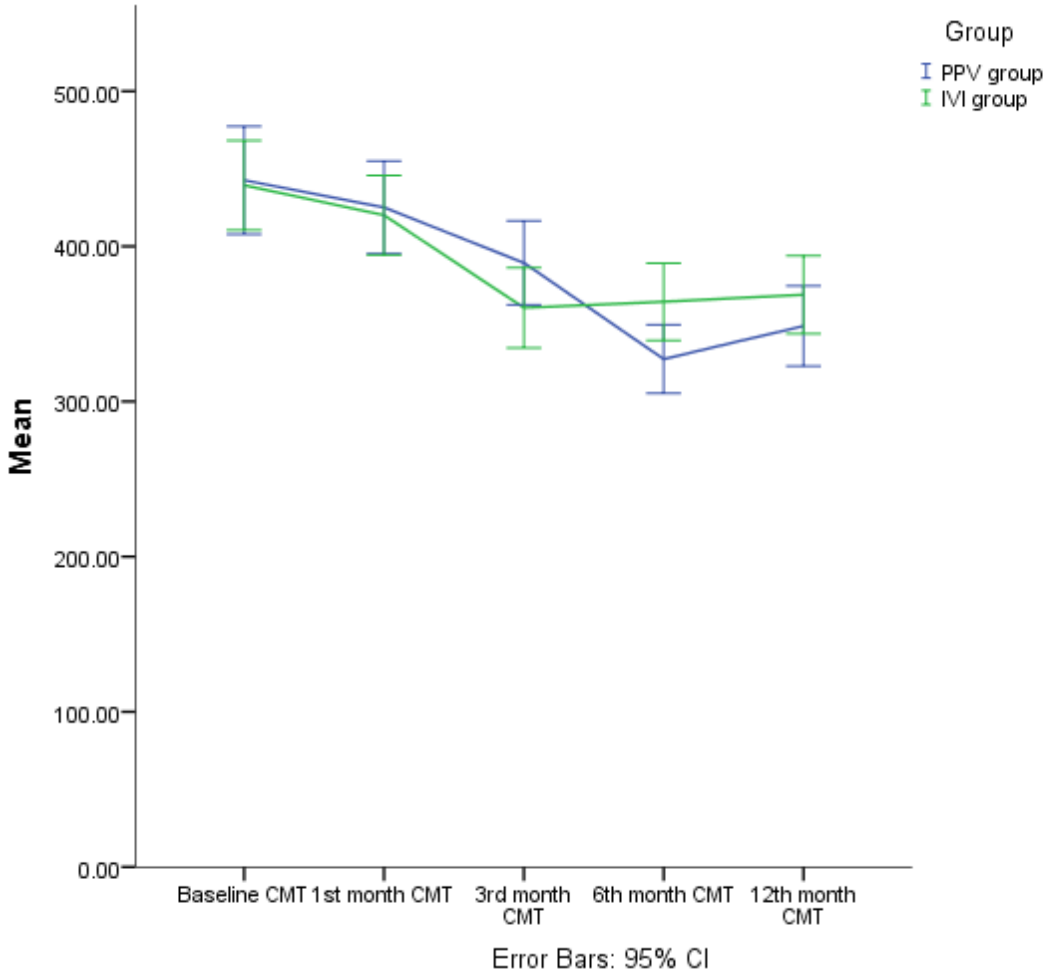

Figure 9 Mean CMT in both groups [µm].

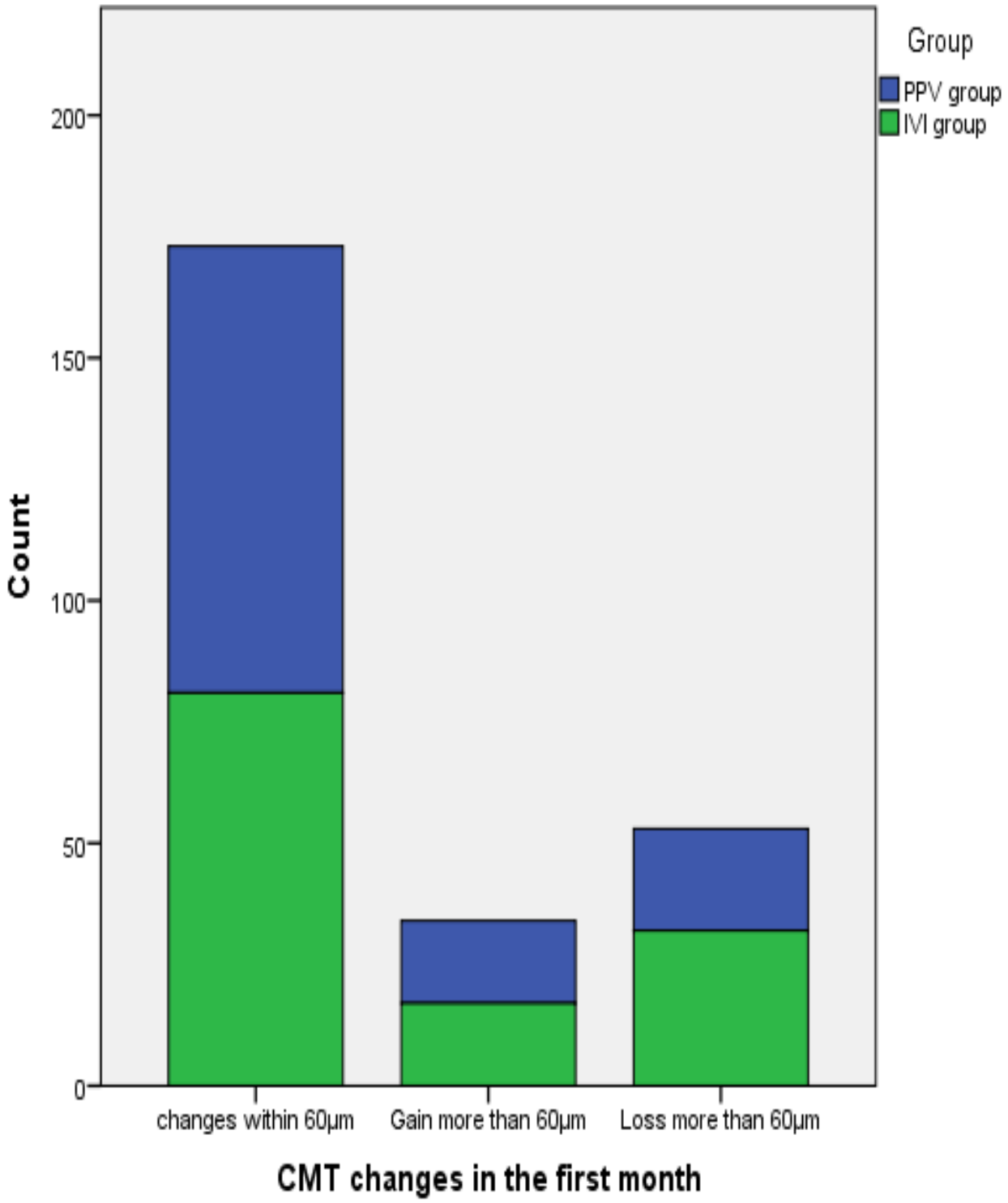

Figure 10 CMT changes in the first month in both groups

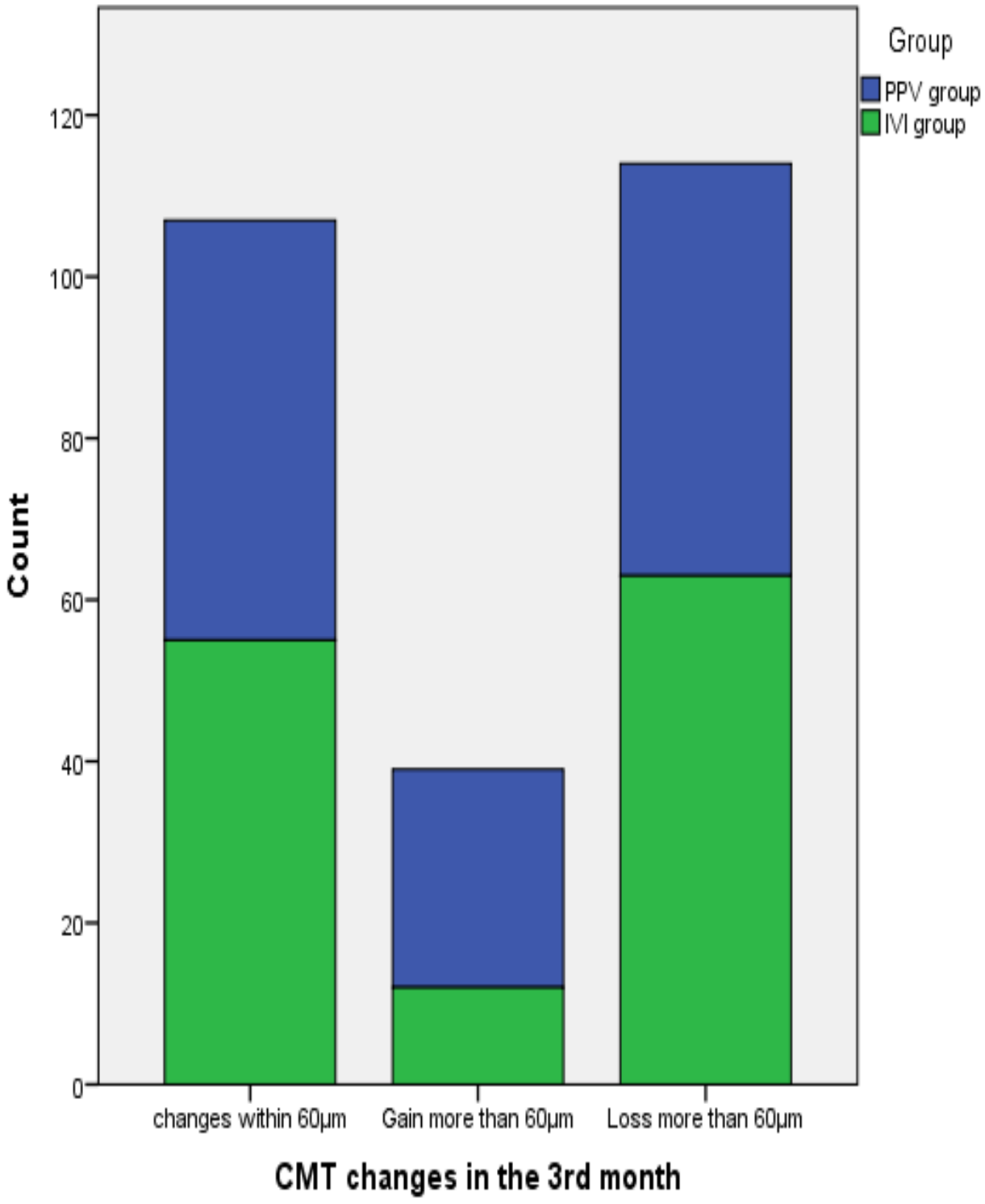

Figure 11 CMT changes in the third month in both groups

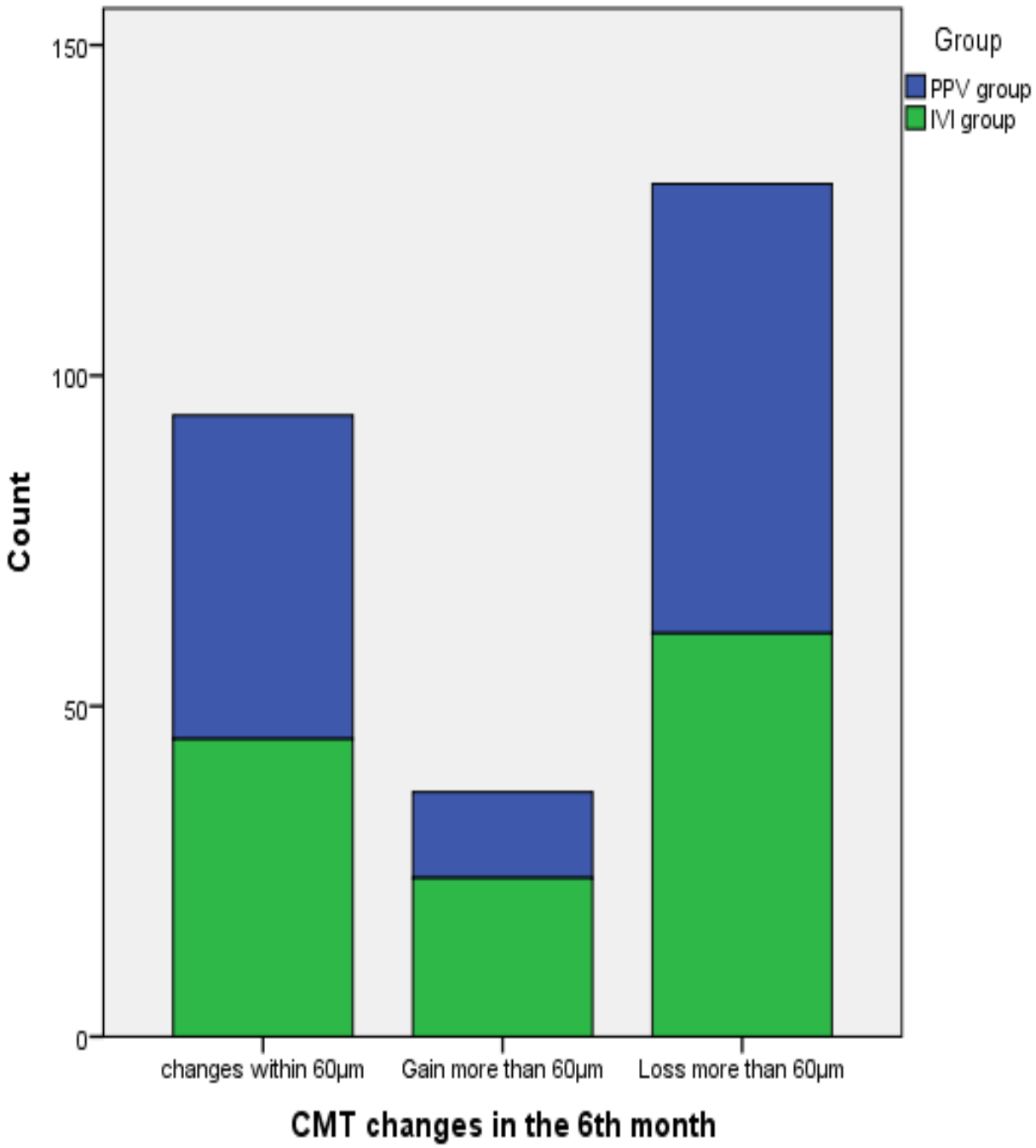

Figure 12 CMT changes in the sixth month in both groups

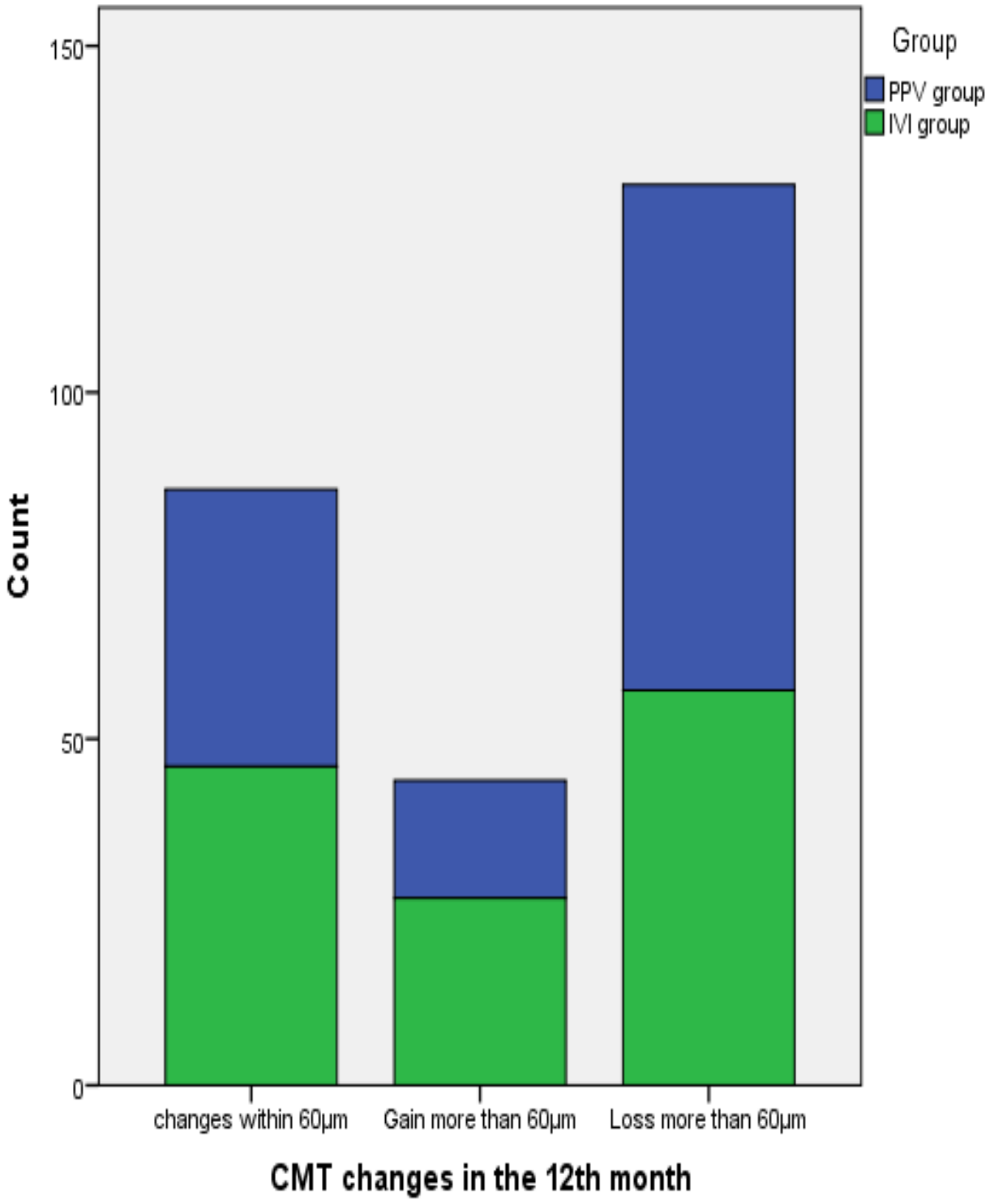

Figure 13 CMT changes in the twelfth month in both groups

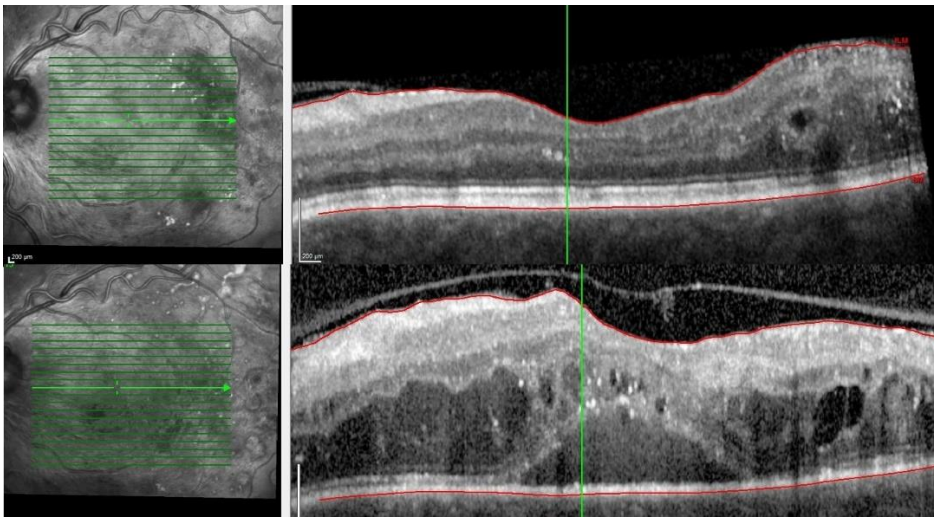

Figure 14 OCT scan showing mild spongy DME before starting IVI (upper) complete PVD, cystoid DME with neurosensory detachment at 12-month post-IVI (lower)

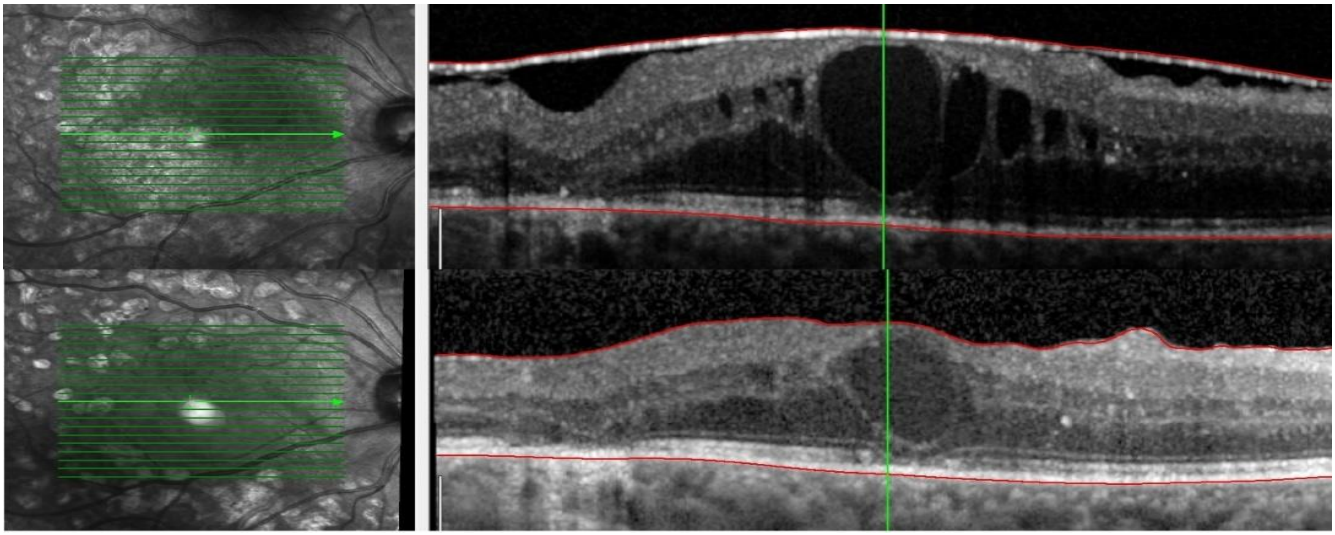

Figure 15 OCT scan showing dense epiretinal membrane with tangential traction and cystoid DME before PPV (upper) reduced DME with macular cyst post PPV (lower)

4.4. Postoperative complications

Intra-operative bleeding with preoperative intravitreal bevacizumab occurred in 6 eyes compared to 10 eyes without intravitreal bevacizumab. Post-operative bleeding occurred in 3 eyes during the first month in intravitreal bevacizumab subgroup. In contrast to vitrectomy without intravitreal bevacizumab 8 eyes had re-bleeding in the 1-month, 2 eyes in the 3-month, 2 eyes in the 6-month and 1 eye in the 12-month follow-up period. However, postoperative complications were considerably higher in PPV group including proliferative vitreoretinopathy (PVR) formation (table 10). Complications in IVI group were uncommon, mainly floaters.

Table 10 Postoperative complications

Characteristics	PPV group (*n*)
Bleeding	13 (10%)
Complicated cataract	15 (11.5%)
Secondary glaucoma	4 (3%)
PVR formation	3 (2.3%)
Re-PPV	5 (3.8%)
Abnormal AC contents	
Si Oil	3(2.3%)
PFCL	1(0.7%)
Hyphema	1(0.7%)

Abbreviations: PPV=proliferative vitreoretinopathy, Si Oil=silicon oil, PFCL=perfluorocarbon liquid

5. Discussion

The choice of treatment when dealing with DME has been complicated in recent years with the emergence of new therapies, which allow for a large number of possible treatment schedules and combinations. Macular laser photocoagulation, subthreshold micropulse diode laser photocoagulation, intravitreal injection of triamcinolone acetonide, dexamethasone intravitreal implant, posterior sub-tenon injection of triamcinolone acetonide, intravitreal injection of anti-VEGF, vitrectomy with/without internal limiting membrane peeling or a combination of these therapies was widely used for DME.

The vast increase in the number of patients undergoing intravitreal treatment and the role of anti-VEGF pharmacotherapy as the mainstay of DME treatment has triggered several challenges. These include considerations regarding the impact of long-term intravitreal treatment to both society and diabetic patients, the cost and the cost-effectiveness of the treatment, as compared to alternative therapeutic approaches. Intravitreal treatment requires long-term follow-up of the patient.

DME cases had almost twice the mean number of total health care visit days compared to non-DME controls (28.6 vs. 16.9 days).[55] The growing incidences of diabetes across the globe further increase the burden of DME. An additional issue to be considered is the number of treatments per eye.[56]

In our study, patients treated with vitrectomy and internal limiting membrane peeling received a mean of 1 treatment per 12 months. In contrast, patients treated with anti-VEGF injections received a mean treatment of 4.6 per 12 months (Table 9).

According to protocol T, the median number of injections in the aflibercept, bevacizumab, and ranibizumab groups over 2 years was 15, 16, and 15, respectively.

Anti-VEGF therapy is being dosed less frequently in clinical practice compared with clinical trials, and the difference in treatment limits visual outcomes.[47]

The number of treatments per year is very crucial, especially in type 2 diabetic patients. These patients are subjected to significant lapses in follow-up because of illness, financial hardship, or noncompliance.

Obeid et al studied loss to follow-up in patients with PDR after panretinal photocoagulation or intravitreal Anti-VEGF injections. They concluded that a large proportion of patients with PDR were "loss to follow-up" after receiving PRP or an anti-VEGF injection over approximately 4 years. Additionally, eyes with PDR that received only intravitreal anti-VEGF demonstrated worse anatomic and functional outcomes after being loss to follow-up compared with eyes that received PRP. Given the potential sequelae of being loss to follow-up. The choice of treatment for PDR must be considered carefully.[57]

Ron Adelman et al reported if only a single therapy is to be considered to treat DME, vitrectomy with internal limiting membrane peeling may be a good option for attaining visual acuity improvement over 24-month follow-up.[58]

In our study, at the time of intervention, the duration of DM in both groups was relatively similar, 14 ± 8 years in PPV group, and 13 ± 6 years in IVI group (Table 2, Figure 3). The prevalence of PDR in PPV group (110 patients (85%)) was higher than IVI group (57 patients (44%)). Additionally, PPV group had considerable macular ischemia in 13 cases (Table 3, 5). Consequently, these eyes may be refractory to vitrectomy for the same reason that they are refractory to anti-VEGF agents. It is quite likely that vitrectomy and its resultant decrease in macular edema would lead to better final BCVA in eyes without much structural damage and it could be beneficial to start a proactive regiment for vitrectomy in cases of no response to intravitreal injection.

Before the era of intravitreal injections, vitrectomy was considered much earlier in the course of DME because there were no other treatment alternatives available for refractory DME. Therefore, eyes with a favorable prognosis, with less macular ischemia and less irreversible macular damage, were operated earlier. Consequently, these patients experienced better visual outcomes.

Our rationale supports vitrectomy in DME and theorizes that in the absence of the vitreous gel, DME:

- Would resolve faster or have a more benign course.
- Would stop progressing or have a slower progression.
- Would not recur or have a lower risk of recurrence.
- Patients would have a risk of loss to follow-up.

In our study, the mean baseline BCVA LogMAR in PPV group was (1.08 ± 0.64) which is relatively less than the mean in IVI group (0.49 ± 0.39) (Table 4). The mean 12-month BCVA in PPV group improved compared to the baseline significantly (Figure 8). However, the final BCVA was lower than IVI group (nearby 0.37 LogMAR improvement in PPV vs. 0.07 in IVI group).

A reasonable explanation is early-onset intravitreal injection compared to late vitrectomy in the course of DME. Furthermore, vitrectomy had been performed in eyes that had experienced repeated injections (20 patients in PPV group had intravitreal injections before vitrectomy) and laser (Table 2, 5). These patients by the time of vitrectomy had indeed long-standing DME without significant improvement. Also, reduced BCVA in PPV group in the first month (Figure 5) with later improvement at 3rd month (Figure 6),6th month (Figure 7) and 12th month (Figure 8) postoperatively can be explained by the presence of intraocular gas tamponade in most of our patients (Table 8).

Our results agree with Ron Adelman et al. They reported initial visual acuity in eyes received pars plana vitrectomy was lower than in all the other treatment groups including anti-VEGF, laser, and steroid. Pars plana vitrectomy with internal limiting membrane peeling resulted in a trend line displaying marked visual recovery about 2-3 times higher when compared to anti-VEGF therapy alone. This result was superior to all other treatment groups including anti-VEGF, laser, and steroid. The improvement in visual acuity continued to increase between 12 and 24 months after surgery. [58]

In our study, a potential study weakness is that the significant difference in the baseline BCVA in both groups which can be compensated by the rate of change of BCVA in both groups.

Improvement of BCVA in PPV group in most but not all eyes was parallel to the reduction of the central macular thickness (Figure 4, 9). The improvement in BCVA was observed at 3rd month (Figure 6), 6th month (Figure 7) and 12th month follow up (Figure 8).

In our study, a reversal of continuous increase in macular thickness, as well as macular function, was observed in PPV group during the follow-up period (Figure 6). Following vitrectomy, especially in eyes that had received previous IVI, the progressive loss of VA stopped in most of our cases. By the end of the 12-month follow-up, the gain of more than 3 lines was more evident in PPV group compared to IVI group (Figure 5).

In PPV group, the visual outcome at 12-month between phakic and pseudophakic eyes revealed improvement in BCVA in both subgroups. Also, the visual outcome improved in both tractional and non-tractional DME at the 12-month follow-up compared to the baseline (Table 5).

In PPV group, ischemic maculopathy demonstrated by FFA was recorded in 13 cases with significant visual improvement at 12-month (Table 5). Chung et al defined patients with an enlarged foveal avascular zone or a broken perifoveal capillary ring at the borders of the foveal avascular zone, with a distinct area of capillary nonperfusion within one disc diameter of the foveal center in the transit phase of fluorescein angiography, as patients

having macular ischemia.[59] This highlights the current role of FFA in the pre-operative assessment of DME and maybe in the future the OCT angiography which would provide more details about capillary perfusion in the area of the fovea.

Our results agree with the current literature supporting vitrectomy for DME and improvement of final visual acuity compared to the baseline.

Jahn and colleagues carried out vitrectomy in 30 eyes of 21 consecutive patients with type 2 DM suffering from DME. The authors reported improvement of visual acuity in eyes with DME after treatment with vitrectomy and the gains in visual acuity were permanent in almost all of the eyes throughout the observation period extending as far as 5 years.[60] Consequently, the effect of vitrectomy is long-lasting compared to intravitreal injection in which patients tend to inject for a relatively longer period.

Also, Browning and colleagues demonstrated that vitrectomy consistently improves center-involving DME and that the median 12-month post-vitrectomy VA improved by 0.20 LogMAR.[61]

Additionally, Haller and colleagues performed vitrectomy in 87 eyes with DME and vitreomacular traction, postoperative reduced retinal thickening was observed in most eyes. Improvement of visual acuity between 28% and 49% of eyes during the follow up for one year.[5]

While the benefits of vitrectomy in patients with non-tractional DME is relatively less clear and debatable. Our results revealed significant visual improvement and central macular thickness reduction in non-tractional DME with internal limiting membrane peeling at a 12-month follow-up (Table 6, 7). The changes in central macular thickness ± 60 μm in both groups during the entire follow up period were comparable and the gain in central macular thickness ≥ 60 μm was more evident in IVI group (Figure 14).

Kumagai and colleagues reported visual gains in 332 consecutive patients with DME without a thickened and taut posterior hyaloid.[62]

Also, Ulrich retrospectively reviewed 42 diabetic patients that underwent vitrectomy with internal limiting membrane for non-tractional DME and reported improved retinal anatomy and visual acuity in patients with non-tractional DME.[63] Moreover, our results support the suggestion by Kim and colleagues that vitrectomy for non-tractional DME refractory to non-surgical therapies including anti-VEGF therapy is an effective treatment modality.[64]

In contrast to our study, Hoerauf and colleagues reported no improved visual acuity in patients with DM type 2 and cystoid DME without evident vitreoretinal traction following vitrectomy, posterior vitreous detachment with or without internal limiting membrane removal. internal limiting membrane delamination showed improved morphological results and seemed to be beneficial in eyes with preexisting posterior vitreous detachment.[65]

Also, Ghassemi and colleagues evaluated prospectively the efficacy of vitrectomy, membranectomy, and internal limiting membrane peeling on the central macular thickness and BCVA in patients with refractory DME and non-tractional epiretinal membrane. The results did not show significant improvement of BCVA in eyes with refractory DME and non-tractional epiretinal membrane despite central macular thickness reduction.[66]

Also, Simunovic and colleagues published a systematic review and meta-analysis on the outcomes of vitrectomy for DME and concluded that there is little evidence to support vitrectomy as a treatment for DME in the absence of epiretinal membrane or vitreomacular traction and that although vitrectomy appears to be superior to laser in its effects on the retinal structure at 6-month, no such benefit has been proven at 12-month. Despite these findings, the role of vitrectomy in the treatment of DME without vitreomacular traction cannot be entirely ruled out.[67]

Our VA results agree with many of the previously published reports [68,69], but not others.[5,70] A reasonable explanation for the inconsistent results in the literature includes heterogenicity of the operated patients, duration of DME, the heterogenicity of the performed procedure, and the stage of diabetic retinopathy when vitrectomy was performed.

We suppose that DME eyes with better prognosis-with intact photoreceptors and better pretreatment BCVA-tend to achieve better visual acuity after vitrectomy. OCT affords good anatomic predictors of the visual acuity response to vitrectomy in DME.

In our study, we classified the pattern of DME into simple thickening, cystoid thickening, and neuroepithelial detachment. We categorized these data depending upon the relative size of the largest cyst in relation to the maximum thickness of the macula. Patients with neuroepithelial detachment had visually significant improvement in visual acuity (Table 7). We assumed that fluid accumulation in cystoid spaces determines the progression of macular edema and the presence of epiretinal membrane and vitreomacular traction raise the indication for vitrectomy with internal limiting membrane peeling (Table 3).

In our result, we observed reduction of central macular thickness in both PPV group and IVI group at 6-month (Figure 12) 12-month follow up (Figure 13) compared to the baseline (Figure 9). The effect of vitrectomy on central macular thickness consisted of flattening of the macula in most eyes (Figure 15). Even without a taut posterior hyaloid or an epiretinal membrane preoperatively, reduction of central macular thickness was demonstrated in some eyes with DME. Additionally, central macular thickness changes in PPV group compared to IVI group revealed a significant reduction of CMT at 1- (Figure 10), 3- (Figure 11), 6- (Figure 12), and 12- month (Figure 13) respectively.

Sakamoto and colleagues reported that better final visual acuity is achieved in eyes with a complete inner segment/outer segment (IS/OS) junction.[71] Also, Yanyali and colleagues found that the integrity of the external limiting membrane and IS/OS lines on OCT strongly correlated with better postoperative visual acuity recovery.[72] These factors are related to the duration of edema before vitrectomy.

Ichiyama and colleagues investigated the effectiveness of vitrectomy for diffuse diabetic macular edema and its dependence on OCT findings. The study retrospectively reviewed the records of 65 patients and 81 eyes who received vitrectomy for diffuse DME and followed up for at least 6 months. All eyes were classified according to their morphological characteristics on OCT. BCVA and spectral-domain OCT were investigated preoperatively and at 1-, 3-, and 6-month postoperatively and they concluded that vitrectomy can be a useful treatment alternative for diffuse DME, particularly for eyes with subretinal fluid. [73]

Our results agree with Ichiyama and colleagues. We found a statistical difference between the different morphological classification of DME regarding the final visual outcome in PPV group compared to the baseline (Table 7). Our surgical technique of vitrectomy with internal limiting membrane peeling offered a better chance for DME resolution and significant improvement in BCVA. We chose to apply panretinal photocoagulation ± cryocoagulation in all cases to reduce the level of intraocular VEGF and to treat the peripheral non-vascularized retina.

It is probable that internal limiting membrane peeling removes invisible residual traction, which is not removed during the routine vitrectomy. This interpretation is supported by the results of a study with 61 specimens of internal limiting membrane and epimacular tissue in patients with DME undergone a histological examination of vitreoretinal tissue. Thickened premacular cortical vitreous was found in 47 eyes. The

epimacular membrane was found in 23 eyes. The study reported a higher incidence of complete posterior vitreous detachment in patients with non-proliferative diabetic retinopathy versus those with PDR, emphasizing the importance of the vitreous in the development and progression of diabetic retinopathy.[74]

Our results agree with most of the previous data, which have consistently shown reduction of the central macular thickness accompanied by improvement of BCVA after internal limiting membrane peeling. However, the improvement of visual acuity following internal limiting membrane removal had mixed results.

Kumagai and colleagues found that internal limiting membrane peeling accelerated the absorption of edema in severe DME but did not further improve visual acuity,[75] while other reports demonstrated that vitrectomy with internal limiting membrane removal provides better visual and morphological results than the natural course.[76,77] However, other studies pointed out, a reduction of macular edema did not consequently lead to a better visual acuity.[78]

We considered preoperative reduced dose intravitreal bevacizumab to decrease the intraoperative bleeding and to a lesser extent to reduce the early postoperative bleeding (Table 8, 10). The dose and the timing of intravitreal injection were consistent with that principle and not to treat the DME.

Patients with PDR featuring neovascularization and fibrous proliferation is one of the foremost diseases that can lead to blindness if not properly treated. One of the most

challenging complications is intraoperative bleeding, which makes vitrectomy very difficult because of poor visualization and requires the use of more equipment.

All of these factors can prolong the total surgical time and hinder surgical outcomes. Moreover, massive bleeding during surgery may even be uncontrollable, leading to surgical failure. For vitrectomy in DME patients with PDR, especially in patients with active neovascularization and/or extensive or multiple layers of fibrovascular proliferation, preoperative intravitreal bevacizumab injections are thus expected to be helpful. The use of preoperative intravitreal bevacizumab was reported to reduce the vascular component of the proliferation in PDR case.[79]

In our study, the preoperative intravitreal bevacizumab subgroup had less intraoperative and postoperative bleeding compared to patients who did not receive preoperative intravitreal bevacizumab.

Zhang and colleagues published a systematic review and meta-analysis on vitrectomy with or without preoperative intravitreal bevacizumab for PDR and concluded that intravitreal bevacizumab before vitrectomy in PDR patients significantly enhanced the procedure, decreased intraoperative complications, and reduced early postoperative hemorrhage.[80] Our study demonstrated reduced both intra- and postoperative bleeding in intravitreal bevacizumab subgroup compared to vitrectomy without intravitreal bevacizumab.

Postoperative complications were mainly observed in PPV group compared to IVI group (Table 10). Our operative complication rate is low and similar to what has been reported for this procedure. Postoperative major complications included PVR (2.3%), re-PPV (3.8%) and complicated cataract (11.5%).

However, intravitreal injection is not a complication-free procedure. In large a clinical trial to evaluate efficacy and safety of intravitreal ranibizumab vs panretinal photocoagulation (PRP groups) over 5 years for PDR. Retinal detachment was identified in 12 and 30 eyes in the ranibizumab and PRP groups, respectively. This must be considered in decision making and treatment plan should be tailored according to patient general health and compliance.[81]

Obied et al reported a significantly greater number of eyes with tractional retinal detachment in the IVI group compared with the PRP group at the end of 4 years follow up in the treatment course of DME.[82]

Jackson and colleagues studied the safety of vitrectomy in DME and concluded that the most frequent complications were a retinal break (7.1%), elevated intraocular pressure (5.2%), epiretinal membrane (3.3%), and vitreous hemorrhage (2.4%). Cataract developed in 68.6% of 121 phakic eyes.[83]

Patient with DME could be considered for vitrectomy in the following situations:

- If the patient developed obvious vitreo-foveal traction or the presence of a macular epiretinal membrane on preoperative OCT scans.
- Intravitreal injection patients who developed ischemia (Ischemic maculopathy).
- Refractory DME.
- The presence of co-morbidity factors and liability to loss to follow up.
- High-risk PDR with ischemia.

6. Conclusion

Vitrectomy with internal limiting membrane peeling is a cost-effective procedure that consistently results in central macular thickness reduction and leads to clinically significant improvement in BCVA comparable to serial intravitreal injection of anti-VEGF. Preoperative OCT assessment is a critical step in the decision-making process. Preoperative intravitreal bevacizumab was associated with reduced intraocular bleeding intra- and postoperatively. A large, comparative, prospective, randomized clinical trial of these two treatments is needed to determine which therapy is more effective.

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8. Scientific Contribution

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