Intravitreal injection of bevacizumab in diabetic macular edema versus vitrectomy with internal limiting membrane peeling with bevacizumab as an adjuvant

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Abstract: Purpose: To evaluate the functional and anatomical outcome of pars plana vitrectomy (PPV) in diabetic macular edema (DME) with pre-operative intravitreal bevacizumab (IVB). **Methods:** This was a prospective study between 2017 and 2018. We included 30 eyes of 30 patients (median age 60 ± 12 years) with type II diabetes mellitus suffering from DME (central macular thickness (CMT) ≥ 300 µm. 15 eyes treated with pars plana vitrectomy (PPV group) with preoperative IVB, and 15 eyes received intravitreal bevacizumab (B group). The best-corrected visual acuity (BCVA) and CMT were investigated at baseline and at 1, 3 and 6 months postoperatively. Also, the number of intraoperative coagulation spots and the incidence of post- vitrectomy hemorrhage at one month postoperative to evaluate IVB. **Results:** 41%, 33% of patients gained more than two lines on Snellen's chart in PPV and IVI group ($p < 0.001$). 31%, 20% decreased by one Snellen line in one eye in PPV and B group ($p < 0.001$). Average CMT decreased from 469 ± 48 µm to 350 ± 19 µm at the end of follow up period ($p < 0.001$) in PPV group and from 541 ± 23 µm to 328±17 µm in B group ($p < 0.001$). Preoperative IVB reduced intraoperative and postoperative bleeding. **Conclusion:** Vitrectomy may result in satisfactory functional and anatomical results in the treatment of DME and may be more convenient than multiple intravitreal bevacizumab injections. Preoperative IVB reduce intraoperative and postoperative bleeding.

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1. Introduction

Diabetic macular edema is one of the major causes of visual impairment in diabetic patients. During the past few decades, dramatic improvement occurred in diagnostic and therapeutic modalities in diabetic retinopathy.[1] The diagnosis of macular edema is based on binocular slit- lamp biomicroscopy, leakage on fundus fluoresce in angiography (FFA), and information on retinal structure and thickness obtained by optical coherence tomography (OCT). Prior to the use of the intravitreal injection approach, laser photocoagulation has represented the mainstay for the treatment of DME.[2] Currently, anti-vascular endothelial growth factor (VEGF) therapy is considered first-line treatment in DME.[3] Bevacizumab (Avastin) is an off-label, full-length, monoclonal antibody that inhibits all VEGF forms.[4] The role of PPV in tractional DME seems to be clear.[5] However, the advantages of PPV in nontractional DME patients remains controversial.[6, 7]

2. Patients and Methods

We included 30 eyes from 30 patients suffering from DME prospectively. 15 eyes treated with PPV (PPV group) 15 eyes received intravitreal bevacizumab for 3 months (B group). We included only DM type II and excluded patients with BCVA less than 1.3 LogMAR, a concomitant ocular pathology that may affect the visual potential e.g. glaucoma, previous PPV, age-related macular degeneration. We also excluded patients who had received intravitreal steroid.

Diagnosis of DME was primarily established by slit lamp biomicroscopy, supplemented by FFA (also exclude ischemic maculopathy) and OCT. BCVA and CMT were evaluated preoperatively as well as 1, 3 and 6 months postoperatively. CMT was measured by OCT with the standard protocol of 6 mm radial scan centered at patient fixation point.

19 eyes had DME in the presence of no proliferative diabetic retinopathy (NPDR) and 11 eyes had DME in the presence of proliferative diabetic retinopathy (PDR). Panretinal photocoagulation (PRP) had been carried out in all eyes before PPV. In 8 eyes epiretinal membrane could be detected by OCT. 28 eyes had diffuse DME and 21 eyes had cystoid macular edema. At the time of PPV, all eyes were pseudophakic and all cases had ILM peeling.

In PPV group, standard three-port PPV was carried out together with peeling of ERM and ILM in 15 eyes (all PPV cases). We used Brilliant Blue G dye to stain ILM, air was a tamponading agent in 12/15 cases and silicon oil in 3/15 cases.

Preoperative IVB (1.25mg/0.05ml) was received 3days before vitrectomy. We evaluated intraoperative bleeding as measured by the reduced number of coagulation spots by endodiathermy and postoperative vitreous hemorrhage at one month.

In group B, intravitreal bevacizumab was received monthly for 3 months then injection as needed. Average number of IVB was 3±1 injection over 6 months of follow up.

Data were compared using the student t-test and p-value smaller than 0.05 was considered statistically significant.

3. Results

In our study, 30 eyes of 30 diabetic patients with DME were included. The average age was 60 ± 12 years. Gender distribution of patients shows that there were 19(63%) male and 11(37%) female patients (table 1). There were 18 right eyes (60%) 14 left eyes (40%). The average preoperative CMT was 469 µm, 541 µm in PPV and B group (table 2). The average preoperative BCVA LogMAR was 0.9, 0.6 in PPV and B group (table3). In PPV group at 1 month postoperatively, there was no significant change in either CMT (480 µm, p= 0.71) or visual acuity (0.8, p= 0.28). However, at 3, 6 months postoperatively the central macular thickness had significantly decreased (431 µm, 350 µm) and the visual acuity was improved (0.7, 0.4) ($p < 0.001$).

In B group, there was no significant change in either CMT (490 µm, p= 0.11) or BCVA (0.5, p= 0.23) at 1 month postoperatively. However, at 3 and 6 months postoperatively CMT decreased (403 µm, 328 µm) and BCVA was improved 0.3 ($p <0.001$).

In PPV group, intravitreal bevacizumab was administered 3 days preoperative to patients (n=15) undergoing vitrectomy. Decreased intraoperative bleeding as measured by the reduced number of coagulation spots. 7/15 cases received endodiathermy with average 5±2 coagulation spots and 8/15 cases received no treatment.

Two cases had mild vitreous hemorrhage within one month postoperatively and medical treatment was satisfactory. One eye was excluded from the analysis after developing a retinal detachment 6 weeks after PPV. 2 patients were lost during follow-up at 3 months.

4. Discussion

Diabetic macular edema (DME) is a major cause of visual morbidity in diabetic patients. Recently anti-VEGF therapy has emerged as the first line treatment in DME and many reports support the effect of anti-VEFG.8 Anti-VEGF therapy in DME results in dryness of the macula and regression of new vessel formation. The Major advantages of Anti-VEGF that it is a simple, outpatient procedure, and does not require specialized equipment or personnel. The major drawback of anti-VEGF injections is its short-term effect leading to multiple injections. The economic burden is a real problem, especially in developing countries. Furthermore, some patient show suboptimal response to anti-VEGF and others are resistant.

Vitrectomy has emerged as an effective treatment for tractional DME with good visual and anatomical outcomes. Many reports support the benefit of PPV in DME.9-11 The effect of PPV on the morphology of the macula consisted of flattening of the macula accompanied by removal of any traction forces exerted by ERM or a taut posterior hyaloid. Vitrectomy improves perfusion of the macula, remove VEGF and inflammatory mediators and increase retinal oxygenation. PPV has the advantage of being a single procedure with much lower cost than multiple injections. The disadvantages of PPV are that it is a difficult and long procedure with learning curve. Moreover, PPV requires well-equipped theater and the final visual outcome is affected by many variables like cataract progression.

In our study, the BCVA progressively improved over subsequent intravitreal injections of bevacizumab, and it remained stable until the end of follow up period. Similar improvement in final BCVA was recorded in the PPV group though the improvement in vision was much earlier in B group when compared with PPV group. However, the total gain in BCVA was more in PPV group than in B group. Patients gained more than two lines on Snellen's chart in PPV (41%), and B group (33%).

CMT was significantly decreased in both groups and it was observed that the decrease in CMT was more in PPV group when compared to a decrease in CMT in B group by the end of the follow-up period.

Our results agree with the current literature supporting the reduction of CMT after vitrectomy accompanied by visual improvement.9 12.

In PDR cases, repeated bleeding during vitrectomy may make the operation lengthy. In our study, preoperative IVB was associated with inhibited retinal neovascularization, resulting in decreased intraoperative oozing from neovascularization following membrane dissection and fewer endodiathermy applications.

Also, preoperative IVB reduced early postoperative vitreous hemorrhage (during the first month follow up). Since IVB is removed along with the vitreous during vitrectomy surgery, there is likely little benefit in preoperative IVB in preventing late postoperative vitreous hemorrhage that may occur 4 weeks following vitrectomy.

Conclusion

The gain in visual acuity and the reduction in CMT was more evident after vitrectomy than after intravitreal injection. Preoperative IVB reduce intraoperative bleeding and postoperative vitreous hemorrhage.

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