

Original article

The adjunctive use of pre-operative intravitreal bevacizumab in the setting of proliferative diabetic retinopathy



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Abstract

Purpose: To evaluate the efficacy of pre-operative intravitreal bevacizumab injection on the rate of postoperative vitreous hemorrhage in patients undergoing vitrectomy for complications of proliferative diabetic retinopathy.

Methods: Consecutive retrospective comparative cohort study. Forty eyes of 37 patients who received pre-operative intravitreal bevacizumab 1.25 mg were compared to a similar group of 44 eyes of 44 patients who had undergone vitrectomy surgery prior to the availability and widespread use of pre-operative intravitreal bevacizumab. The primary outcome measure was the incidence of post-vitrectomy hemorrhage at one week after surgery. Secondary outcome measures included are postoperative vitreous hemorrhage at one month and changes in the best-corrected visual acuity (BCVA). For statistical analysis, the paired Student's t-test and Fisher's exact test were used.

Results: Four out of 40 eyes (10%) pretreated with intravitreal bevacizumab vs. 12 of 44 eyes (27%) not pretreated with intravitreal bevacizumab had a clinically significant postoperative vitreous hemorrhage at one week. The mean best-corrected visual acuity (BCVA) in bevacizumab group improved from a mean of hand motions to a mean of 20/300 at 1 month (range: 20/25-light perception; $p < .001$) and mean BCVA in the non-injected group improved from preoperative mean of hand motion to 20/200 at one month follow-up (range: 20/25-no light perception; $p < .001$). In both groups, 4 patients (12%) needed repeat vitrectomy.

Conclusion: There is a trend to reduced incidence of early post-vitrectomy hemorrhage in patients undergoing vitrectomy for complications of proliferative diabetic retinopathy that have been pre-treated with intravitreal bevacizumab 1 week prior to surgery.

Keywords: Bevacizumab, Proliferative diabetic retinopathy, Vitrectomy, Vitreous hemorrhage

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Introduction

Postoperative vitreous hemorrhage after vitrectomy for complications of diabetic retinopathy commonly occurs with

an incidence of 12–63%.^{1–4} Patients with postoperative vitreous hemorrhage suffer a delay in visual recovery while in some patients, this can result in loss of vision and need for reoperation. Although the source is often not identifiable,

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causes of early (or persistent) postoperative vitreous hemorrhage include dispersion of residual blood from the peripheral vitreous skirt or retinal surface, and oozing of blood from dissected fibrovascular tissue or directly from the sclerotomies.^{2,5,6} Sources of late (or recurrent) postoperative vitreous hemorrhage include fibrovascular proliferation from sclerotomy sites and traction from residual fibrovascular tissue.

In an effort to reduce the rate of post-operative vitreous hemorrhage, systemic administration of anti-fibrinolytic drugs,^{7,8} intravitreal thrombin,⁹ and sodium hyaluronate¹⁰ have been tried with relatively little success. Other possible techniques include sclerotomy cryotherapy,¹¹ and intravitreal tamponade with silicone oil,¹² or non-expandable gases (SF₆ and C₃F₈^{13,14}).⁵⁻¹⁶ Bevacizumab (Avastin[®]) is a recombinant monoclonal antibody against vascular endothelial growth factor (VEGF) and has been used in the treatment of proliferative diabetic retinopathy (PDR) and other vascular diseases.^{17,18} It can induce regression of retinal neovascularization in diabetic patients and thereby facilitate fibrovascular membrane dissection and reduce the amount of intraoperative hemorrhage. It may also be used to expedite resolution of non-clearing vitreous hemorrhage (VH).¹⁷ The IVB can also be used as a preoperative adjunct in cases of vitrectomy for complications of diabetes including tractional retinal detachment (TRD) or non-clearing VH to decrease the risk of early postoperative VH.¹⁹⁻²² We retrospectively evaluated our cases of vitrectomy for proliferative diabetic retinopathy to study the effect of pre-operative IVB injection on visual acuity and on the rate of early post vitrectomy hemorrhage.

Materials and methods

This was a consecutive, retrospective, single-centered, single surgeon (PJK) comparative cohort study that was approved by our Institutional Research Ethics Board. The charts of all diabetic patients with complicated PDR undergoing vitrectomy between 2003 and 2009 were identified and reviewed. The routine use of pre-operative intravitreal bevacizumab began in the early 2006. The treated group was drawn from consecutive patients undergoing vitrectomy surgery for complications of proliferative diabetic retinopathy and the control group was chosen from a similar number of a pathology matched cohort undergoing surgery from 2003 to 2005. Eyes with complicated PDR undergoing surgery for non-clearing VH or TRD involving or threatening the macula (with or without a rhegmatogenous component) were included for analysis. Eyes undergoing vitrectomy for reasons unrelated to complications of PDR, including chronic macular edema, epiretinal membrane, and vitreomacular traction, were excluded. Patient characteristics including age, sex, visual acuity, history or pan-retinal photocoagulation (PRP), prior intraocular surgery, use of insulin, macular TRD, and lens status were documented from a review of the patient's chart. The use of endotamponade or the incidence of intraoperative complications was also recorded.

Eyes in the bevacizumab (Avastin) group received an injection at a mean of 11 days after surgery (median = 8 days, range: 1-53 days). All intravitreal injections were administered in a standard fashion after obtaining informed consent. Following administration of topical anesthetic drops, a lid speculum was inserted and topical 2% xylocaine gel applied.

A 10% povidone – iodine swab stick was then used to paint the injection site. Bevacizumab (1.25 mg) in 0.05 mL in a pre-filled syringe was injected using a 30-gauge needle 4 mm posterior to the superotemporal corneoscleral limbus. No injection-related complications were observed.

The surgical procedure was similar for the two groups. All patients underwent a standard 20-gauge or 23-gauge 3-port pars plana vitrectomy (PPV). Following sufficient clearance of the vitreous hemorrhage to allow visualization of the posterior pole when necessary, dissection of the pre-retinal fibrovascular proliferation was carried out using a modified *en bloc* technique. With elevation of the posterior hyaloid, meticulous shaving of the vitreous base under a wide-angle viewing system was performed with careful attention to remove as much residual blood as possible. (Fill-in) panretinal endolaser photocoagulation (PRP) was administered to any area of previously untreated retina. Full attention was directed to relieving all traction. Hemostasis was maintained by raising intraocular pressure, or by administering endolaser or endodiathermy.

The primary outcome measure was the incidence of significant early post-vitrectomy hemorrhage at one week that prevented visualization of the retina. Secondary outcome measures included post-operative vitreous hemorrhage at 1 month, recurrent/persistent vitreous hemorrhage that requires reoperation, and change in best-corrected visual acuity (BCVA).

Descriptive statistics including numbers and percentages of categorical variables, mean and standard deviation for continuous variables were calculated for demographic and clinical characteristics. Group comparisons were performed using the chi-square test (Fisher's exact test whenever indicated). Snellen visual acuity was converted to logarithm of maximum angle of resolution (LogMAR) units for purposes of analysis.

Results

Baseline characteristics

A total of 40 consecutive eyes pretreated with bevacizumab (Avastin) were compared to a similar group of 44 consecutive eyes of patients who had undergone vitrectomy surgery prior to the availability and widespread use of bevacizumab. A comparison of the baseline characteristics of the two groups is given in Table 1.

Table 1. Baseline patient characteristics.

| | Bevacizumab group | Untreated group | p value |
|-------------------------|-------------------|-----------------|------------|
| Number of eyes | 40 | 44 | |
| Age (years) | | | p>0.05 |
| Mean | 56.4 | 63.13 | |
| Range | (27-83) | (27-90) | |
| Prior PRP | 33 | 27 | p = 0.520 |
| Lens status | | | |
| Phakic | 27 | 32 | |
| Pseudophakic or Aphakic | 13 | 12 | p = 0.6393 |
| Use of insulin | 26 | 25 | p = 0.506 |
| Macular TRD | 5 | 9 | p = 0.3895 |

PRP – Panretinal Photocoagulation.

TRD – Tractional Retinal Detachment.

There was no any statistically significant difference in patient characteristics between the two groups.

Post-operative vitreous hemorrhage

Table 2 summarizes the incidence of early post-vitreotomy vitreous hemorrhage and the number of patients who required re-operation because of persistent vitreous hemorrhage.

At one week post-operatively, 4 (10%) in the bevacizumab group had VH whereas 12 (27.2%) in the control group had VH ($p = 0.054$). Despite the trend of reduced risk in the treatment group, the difference was not statistically significant. At one month, 7 (17.5%) in the bevacizumab group and 9 (21.9%) in the control group had a significant VH ($p = 0.781$); this difference was not statistically significant. Three patients in the control group missed their second month post-operative visit so their last observation was carried forward.

Visual acuity

Results of the visual acuity and changes in visual acuity at one month postvitrectomy are detailed in Table 3. In the bevacizumab group, the mean BCVA at baseline was hand motion (HM) and at one month was 20/300 (mean change in LogMAR = -1.014) which is a statistically significant improvement. In the control group, the mean BCVA at baseline was HM and at one month was 20/200 (mean change in LogMAR = -0.8790) which was also a statistically significant improvement.

An independent 2-sample *t*-test comparing the change in visual acuity at one month in the two groups determined that there was no statistically significant difference between the two groups ($p = 0.594$).

Discussion

Early post-vitreotomy hemorrhage can delay visual recovery in patients who likely already have limited vision in their contralateral eye and prevent any necessary post-operative retinal treatment that may be needed including additional laser treatment, with the risk of worsening foveal function in the long-term.

The effects of bevacizumab on retinal neovascularization secondary to diabetic retinopathy have been evaluated in a number of studies.^{16,17} Avery et al. showed partial or complete reduction of leakage from the foci of neovascularization on fluorescein angiography within one week after intravitreal injection of bevacizumab in 45 eyes with PDR.¹⁶ Similar studies¹⁹⁻²³ have suggested that IVB may reduce the incidence of intraoperative and postoperative vitreous hemorrhage in the setting of diabetic vitrectomy by inducing regression of retinal neovascularization which may facilitate fibrovascular membrane dissection and consequently reduce intraoperative hemorrhage. In addition, IVB may reduce postoperative vascular oozing from neovascular stumps following operative dissection of fibrovascular tissue. Since IVB is removed along with the vitreous during vitrectomy surgery, there is likely little benefit in pre-operative IVB in preventing post-operative reproliferation that may occur weeks following vitrectomy surgery. This may explain our observation that there was a reduction in the incidence of early postoperative vitreous hemorrhage in eyes pre-treated with IVB but no difference in the incidence of delayed post-operative vitreous hemorrhage or a reduced need for reoperation.

Our study showed no statistically significant difference between pretreated eyes and untreated eyes. This is similar to reports by Lo et al.¹⁹ who compared 33 eyes pretreated with bevacizumab and 104 untreated eyes and found no statistically significant difference between the two groups for postoperative VH and final visual acuity with an overall incidence of postvitrectomy VH of 13%. Romano et al.²⁰ performed a non-controlled prospective study on 32 eyes with non-clearing VH resulting from active PDR, in which bevacizumab 2.5 mg was injected one week before vitrectomy. The rate of VH recurrence was 3% at one week and one month follow-up. In a prospective comparative study of 22 patients, Rizzo et al.²¹ reported that pre-operative bevacizumab reduces neovascularization and facilitates vitrectomy. Mean BCVA improvement in the pretreated group at the 6-month follow-up was better than that in the control group although this difference did not reach up to the statistical significance threshold. The authors also showed decreased surgical time and less need for intraoperative tool exchange in the treated group.

Some studies, on the other hand, demonstrate benefit to pre-operative IVB. Ahmadiéh et al.²² demonstrated in a randomized, double-masked clinical trial of 68 eyes that IVB injection before vitrectomy decreases the incidence of early VH in high risk PDR. In spite of the significant difference between the two groups, it can be argued that their patient population is different, which might reflect different response to pre-treatment with bevacizumab. In another prospective randomized study conducted on 72 eyes, Di Lauro et al. found a significant reduction in early postvitrectomy VH (3 months follow-up) in eyes that IVB 7 and 20 days before surgery.²³ However, a significant number of eyes received silicone oil tamponade and were not excluded before the statistical analysis was performed, which confounded the occurrence of post-vitreotomy VH. Modarres also concluded that IVB facilitates surgery despite the high number of silicone oil tamponade in his series.²⁴

The reported incidence of post-vitreotomy VH for complicated PDR in recent studies^{23,24} is less than^{1,2} in studies that were published more than 25 years ago. Although direct

Table 2. Early postoperative VH.

| | Bevacizumab group | Untreated group | P-value |
|---------------------|-------------------|-----------------|--------------|
| Number of eyes | 40 | 44 | |
| VH at one week | 4 (10%) | 12 (27.2%) | $p = 0.0545$ |
| VH at one month | 7 (17.5%) | 9/41 (21.9%) | $p = 0.7813$ |
| Repeated vitrectomy | 4 (10%) | 4/41 (9.8%) | $p = 0.738$ |

Table 3. Visual acuity at one month.

| | Bevacizumab group | Untreated group | p value |
|-------------------------|-------------------|-----------------|--------------|
| Preoperative | HM | HM | $p = 0.3049$ |
| One month postoperative | 20/300 | 20/200 | $p = 0.594$ |
| Difference in LogMAR | -1.014 | -0.8790 | |

comparison of incidence rates among different studies is difficult, this likely reflects intervening advances in modern vitrectomy surgery. To minimize this bias, we strove to include only those patients operated on in the same modern small gauge vitrectomy era, that is to say those operated on in the 3 years immediately before the availability and widespread use of pre-operative IVB and those undergoing surgery in the 3 years immediately following the introduction of adjunctive IVB.

In the present study, both groups showed significant improvement in BCVA but the difference in the improvement of BCVA between the two groups was not significant ($p = 0.5942$). This is in agreement with other studies.^{19–23} Modarres et al.²⁴ showed significant differences between the pre- and post-operative BCVA, in both the control and treatment groups at last follow-up. In addition, the injected group had better visual acuities than the control group.

One possible complication of IVB injection in PDR is aggravation of fibrosis. In a report by Arevalo et al.,²⁵ TRD occurred in 11 of 211 eyes (5.2%) with severe PDR pretreated with an intravitreal injection of bevacizumab more than a week before the surgery. We did not encounter this complication in our series and believe that it can largely be avoided by injecting patients not more than 1 week pre-operatively.

A major drawback in this comparative series is its retrospective nature, and the fact that the comparison groups were non-randomized, and non-contemporaneous which might generate bias and allow confounding factors to mask the true effect of IVB injections in facilitating surgery and limiting postvitrectomy hemorrhage and complications.

Post-vitrectomy VH is a significant complication following vitrectomy for the treatment of PDR and remains a major cause of morbidity. It not only delays visual recovery but can lead to the need for re-operation further exposing the patient to additional risk and anxiety and adding to the overall cost of care. The adjunctive use of the IVB 7 days before vitrectomy for complicated PDR may decrease the incidence of early post-vitrectomy VH.

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Conflict of interest

The authors declared that there is no conflict of interest.

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