

# Perioperative Use of Bevacizumab in Vitrectomy for Proliferative Diabetic Retinopathy: A Literature review

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## Abstract

**Purpose:** To review the effectiveness and safety of perioperative injection of bevacizumab in vitrectomy for proliferative diabetic retinopathy (PDR)

**Methods:** A literature search of all English articles from the Medline and Scopus databases was performed. Original articles, case reports and letters were included.

**Results:** Nineteen, 3 and 5 studies reported preoperative, intraoperative and postoperative intravitreal injection of bevacizumab, respectively. There are good evidences that preoperative injection of bevacizumab induces the regression of new vessels, facilitates the surgery and may reduce the incidence of postoperative vitreous hemorrhage in selected eyes. Also, it may decrease the vitreous clear up time for postoperative vitreous hemorrhage. However, the risk of development or progression of tractional retinal detachment (TRD) should be considered. Postoperative complications like the neovascular glaucoma and nonclearing vitreous hemorrhage may be properly managed by intraocular bevacizumab injection.

**Conclusion:** Preoperative intravitreal bevacizumab (IVB) seems to be effective and relatively safe for surgical facility with variable effects on postoperative hemorrhage. Postoperative intravitreal injection may be effective for the treatment of postoperative complications.

**Keywords:** Anti-Vascular Endothelial Growth Factor, Bevacizumab, Avastin, Proliferative Diabetic Retinopathy, Vitrectomy

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## Introduction

Vitreoretinal surgery for advanced proliferative diabetic retinopathy (PDR) is often complicated by hemorrhage from fibrovascular tissue. Massive intraoperative hemorrhage before proper release of the traction is a major cause of surgical failure. Despite appropriate maneuvers for control of hemorrhage, in some cases, repeated bleeding from multiple sites may make the operation lengthy and tedious.<sup>1,2</sup> Also, postvitrectomy complications like macular edema, vitreous hemorrhage and neovascular glaucoma may compromise the surgical results.<sup>3</sup>

Bevacizumab (Avastin, Genentech, Inc., South San Francisco, CA), is a monoclonal antibody that binds to all VEGF isoforms. It has been approved for the treatment of colorectal cancer by Food and Drug Administration (FDA), but not for intraocular injection.<sup>4,5</sup> Nevertheless, its "off label" intraocular injection has been widely used for the treatment of different ocular diseases associated with neovascularization.<sup>6-10</sup> There are many reports of intravitreal bevacizumab (IVB) being well-tolerated and showing promising results in the treatment of PDR.<sup>8-10</sup> In this article, the recent studies on the use of IVB injection before, during and after vitrectomy for advanced PDR are reviewed.

## Methods

A literature search of all English articles from the Medline and Scopus databases were performed using the keywords "vitrectomy", "proliferative diabetic retinopathy", "Anti-Vascular Endothelial Growth Factor", "bevacizumab", and "Avastin". Original articles, letters, and case reports, from the January 2005 to May 2010 were reviewed. Given the expectation that relevant studies would be quite small, no restrictions were placed on the level of evidence required for inclusion.

## Results

### **Preoperative intravitreal bevacizumab**

Nineteen studies have reported the outcomes of IVB injection before vitrectomy for PDR (Table 1).<sup>11-29</sup> Among these, 13 prospective and 4 retrospective studies were identified. Sixteen studies reported different intraoperative variables for surgical facility

including intraoperative hemorrhage, endodiathermy use, and surgical time, all of them emphasizing facilitation of the surgery after IVB injection.

Eight prospective studies randomized patients to receive IVB or undergo direct surgery without pretreatment.<sup>13,14,20,22,24,25,28,29</sup> Only one study reported enough data about randomization, blinding, statistical analysis and follow-up.<sup>25</sup> All other studies were defective in presenting one or more of the above mentioned quality assessment factors. All studies including one which was specifically designed to measure the red blood cell count during surgery showed a lower rate of intraoperative bleeding. Four study showed a lower rate for endodiathermy use during surgery, however, one study reported similar rates between the two groups despite lower incidence of intraoperative hemorrhage.<sup>25</sup> Six studies reported lower surgical time in the IVB pretreated group and one study didn't find significant difference between the two groups.<sup>22</sup> One study showed higher rate of subretinal hemorrhage during operation on IVB pretreated eyes.<sup>22</sup> Retinal reattachment rate was better in IVB group in one study and similar between the 2 groups in 2 other studies. Two studies reported that the need for silicone oil tamponade was less in IVB pretreated eyes; however, the rates were similar in 4 other studies. Six studies reported better visual outcomes in IVB group and one study showed similar visual results between the two groups.<sup>24</sup> Six studies among those that reported the rate of postoperative vitreous hemorrhage showed a lower rate in the pretreated group. Two studies, however, reported similar vitreous hemorrhage rates between the two groups.<sup>21,23</sup> Two studies showed shorter vitreous clear up time for the pretreated eyes.<sup>16,22</sup>

IVB was administered between 1 to 30 days before surgery. Although some studies didn't report any complication attributable to IVB injection, three studies reported development or progression of tractional retinal detachment (TRD) after injections.<sup>15,21,22</sup> In a retrospective series, Arevalo et al<sup>15</sup> reported that 5.2% of eyes developed or had progression of TRD following IVB injection.

**Table 1.** Intravitreal injection of bevacizumab before vitrectomy for proliferative diabetic retinopathy

Author	Design	Indication	Number of eyes studied	Intervention	Interval between injection and operation (days)	Intraoperative findings	Follow up	Visual outcome	Anatomical outcome	Complication after IVB	comment
Chen and Park <sup>11</sup>	Case report	TRD	1	IVB	7	Minimal bleeding	1 month	Improved	Attached retina	No	
Ishikawa et al <sup>12</sup>	Prospective Case series	Severe PDR	8	IVB	3-30	Minimal bleeding	Not reported	Improved in 7 eyes	Attached retina in all eyes	Strong fibrosis in 2 eyes	
Rizzo et al <sup>13</sup>	Prospective randomized trial	TRD TRRD TRD+VH	22	IVB group: 11 eyes No IVB: 11 eyes	5-7	Shorter operation time Less bleeding Less endodiathermy in IVB group	6 months	Better in IVB group	Better in IVB group	No	
Modarres et al <sup>14</sup>	Prospective randomized trial	TRD TRRD	40	IVB group: 22 eyes No IVB: 18 eyes	3-5	Shorter operation time Less bleeding Less endodiathermy in IVB group	Mean: 7 months	Better in IVB group	One reoperation in each group Less postop vitreous hemorrhage in IVB group	No	
Arevalo et al <sup>15</sup>	Retrospective case series	TRD VH Incomplete regression after PRP	11	IVB	3-31	NA	NA	All operated eyes improved		See comment	Designed to only report TRD development or progression after IVB
Yang et al <sup>16</sup>	Prospective case series with retrospective control	Severe FVP	40	IVB group: 16 eyes No IVB: 24 eyes	7	Less bleeding in IVB group Similar surgical time	6 months	Similar outcome	Retina attached in all eyes Less vitreous clear up time in IVB group	Not reported	
Yeoh et al <sup>17</sup>	Prospective case series	TRD VH with INV	18	IVB	6-14	Minimal endodiathermy	6 months	Improved in 14, stable in one, decreased in 3	38% postoperative vitreous hemorrhage	No	
Yeung et al <sup>18</sup>	Retrospective controlled case series	TRD	69	IVB group: 29 eyes No IVB: 40 eyes	1-23	NA	1 month	Better in IVB group	Less early postoperative vitreous hemorrhage in IVB injected eyes	No	
Romano et al <sup>19</sup>	Prospective case series	VH	32	IVB	4-7	Minimal bleeding	6 months	Improved in 91%	Attached in 97%	No	

da R Lucena et al <sup>20</sup>	Prospective randomized trial	TRD	20	IVB group: 10 eyes No IVB: 10 eyes	14	Less bleeding during surgery in IVB group	NA	NA	NA	No	Designed to evaluate the cassette erythrocyte count
Oshima et al <sup>21</sup>	Retrospective controlled case series	TRD TRRD	61	IVB+MIVS group: 38 eyes No IVB+ 20 gauge vitrectomy: 33 eyes	2-30	Shorter operation time Less bleeding in IVB group	At least 6 months	Similar between 2 groups	Similar between 2 groups	Progression of TRD in 18%	
Yeh et al <sup>22</sup>	Prospective randomized trial	Active PDR with hemorrhage	41	IVB group: 20 eyes No IVB: 21 eyes	7-9	Less bleeding More subretinal hemorrhage in IVB group Similar surgical time	At least 6 months	Better in IVB group	Less postop hemorrhage, less vitreous clearup time	Progression of TRD in one eye	
Lo et al <sup>23</sup>	Retrospective controlled case series	VH TRD TRRD	137	IVB group: 33 eyes No IVB: 104 eyes	1-27	NA	At least 6 weeks	Similar between 2 groups	Similar between 2 groups	No	
El-Batarny <sup>24</sup>	Prospective randomized trial	TRD TRD+VH VH	30	IVB group: 15 eyes No IVB: 15 eyes	5-7	Shorter operation time Less bleeding Less endodiathermy in IVB group	At least 7 months	Similar between 2 groups	Less postop hemorrhage	No	
Ahmadieh et al <sup>25</sup>	Prospective randomized trial	TRD VH Active progression of PDR	68	IVB group: 35 eyes No IVB: 33 eyes	7	Less bleeding in IVB group Similar endodiathermy	1 month	Better in IVB group	Less postop hemorrhage	No	Significant clearing of vitreous hemorrhage in IVB group before operation
Gandhi et al <sup>26</sup>	Case report	Severe PDR	Case report	IVB	14	Minimal bleeding	3 months	Improved	Retina attached	Macular hole	
Hattori et al <sup>27</sup>	Prospective controlled case series	TRD VH	52	IVB group: 12 eyes No IVB: 40 eyes	3	Less endodiathermy In IVB group	NA	NA	NA	NA	Designed to report the effect of lower doses of IVB on VEGF level
di Lauro et al <sup>28</sup>	Prospective randomized trial	TRD VH	72	IVB group: 48 eyes No IVB: 24 eyes	7 or 20	Shorter operation time Less bleeding Less endodiathermy Less silicone tamponade in IVB group	6 months	Better in IVB group	Less postop hemorrhage In IVB group	No	
Hernández-Da Mota, and Nuñez-Solorio <sup>29</sup>	Prospective randomized trial	TRD	40	IVB group: 20 eyes No IVB: 20 eyes	2	Shorter operation time Less bleeding in IVB group	6 months	Better in IVB group		No	

IVB: Intravitreal bevacizumab  
PDR: Proliferative diabetic retinopathy  
TRD: Tractional retinal detachment  
TRRD: Tractional rhegmatogenous retinal detachment  
VH: Vitreous hemorrhage

Time from injection to TRD was a mean of 13 days (range 3-31 days) and 9 out of 11 (81.8%) TRDs developed or progressed 5 days or more after the injection. Oshima et al<sup>21</sup> identified preoperative ring-shaped fibrovascular membrane formation and absence of previous panretinal photocoagulation as the only factors statistically correlated with rapid progression of TRD. Although they didn't find the time interval between injection and operation as a risk factor for TRD progression, based on the Arevalo's finding, other authors suggest that shorter interval is safer.<sup>14,15</sup> The final mean visual acuity (VA) in eyes with progression of the preexisting TRD was worse compared with eyes without this complication.<sup>15</sup> Gandhi et al<sup>26</sup> reported development of a full-thickness macular hole after IVB injection.

Hattori et al<sup>27</sup> showed that lower doses of IVB (as low as 0.16 mg) were as effective as the standard dose (1.25 mg) in reducing vitreous VEGF concentrations and also decreasing intraoperative bleeding.

#### **Intraoperative intravitreal bevacizumab**

In a prospective case series, Romano et al<sup>30</sup> evaluated the recurrence rate of vitreous hemorrhage in 30 eyes that underwent pars plana vitrectomy and IVB injection at the end of vitrectomy. The percentage of severe recurrent VH with no fundus details (grade 3) was 7%, 13%, 27%, and 30%, respectively, at 7 days and 1-, 3-, and 6-month follow-up. They concluded that IVB injection at the end of surgery cannot prevent rebleeding in eyes undergoing pars plana vitrectomy for treatment of diabetic vitreous hemorrhage.

Lee et al<sup>31</sup> reported a case of multiple, extensive panretinal hemorrhages 7 days following pars plana vitrectomy, phacoemulsification with intraocular lens implantation, endolaser photocoagulation and intravitreal injection of 1.25 mg bevacizumab at the end of surgery. Nine months after surgery, retinal hemorrhages were resolved.

In a retrospective comparative study, Park et al<sup>32</sup> evaluated the clinical outcome and complications of IVB versus intravitreal triamcinolone acetonide (IVT) injections at the end of vitrectomy in 156 eyes with diabetic vitreous hemorrhage with or without TRD. The rate of early postoperative vitreous hemorrhage was significantly lower in the IVB

(12.1%) and IVT group (9.1%) than the control group (36.8%,  $P=0.002$  and  $0.006$ , respectively). No significant difference was found in the occurrence of the late vitreous hemorrhage and the reoperation rate was similar between the 3 groups.

#### **Postoperative intravitreal bevacizumab**

Five studies reported the use of IVB for complications occurred after vitrectomy for PDR.

Ruiz-Moreno et al<sup>33</sup> injected IVB to treat recurrent postvitrectomy diabetic vitreous hemorrhages in 4 eyes. In these eyes, two or more episodes of vitreous hemorrhage occurred which did not clear despite two vitreous lavage procedure and more than 2 months of follow-up. No changes in vitreous hemorrhage were observed after a single injection, however, all were cleared completely after 2 or 3 injections. Yeh et al<sup>34</sup> injected IVB in 20 eyes with postoperative recurrent vitreous hemorrhage after primary diabetic vitrectomy. Repeated injections were given after 2-3 weeks in case of no obvious blood reabsorption and 18 eyes with similar condition but no IVB injections were served as controls. Vitreous clear up time after the first recurrent vitreous hemorrhage was  $6.5 \pm 1.5$  weeks with  $2.2 \pm 0.8$  injections in the study group, and  $6.4 \pm 1.3$  weeks in control group, however, the rate of reoperation for vitreous hemorrhage was significantly higher in the control group ( $0/20$  versus  $8/18$ ). Liu et al<sup>35</sup> injected the IVB in 8 eyes with postoperative vitreous hemorrhage after vitrectomy for PDR. Although 4 (50%) eyes had clearance of vitreous hemorrhage, 3 eyes developed ghost cell glaucoma within 1 week after intravitreal injection of bevacizumab. They concluded that caution should be exercised when administering an intravitreal injection of bevacizumab for a postoperative vitreous hemorrhage after vitrectomy for PDR.

Yanyali et al<sup>36</sup> retrospectively reviewed the effect of IVB for persistent diabetic macular edema (DME) in 11 eyes of 10 patients despite prior vitrectomy with internal limiting membrane removal. All eyes had received three intravitreal injections of bevacizumab 1.25 mg/0.05 ml monthly. They didn't find significant changes in VA and foveal thickness in 3 and 6 months.

Falavarjani et al<sup>37</sup> evaluated the effect of intrasilicone injection of bevacizumab for the treatment of 5 eyes with neovascular glaucoma which occurred after vitrectomy for advanced PDR. The iris neovascularization regressed in all eyes and intraocular pressure was controlled within 7 days. In one eye, neovascular glaucoma recurred after 3 months and was successfully treated with reinjection.

### Conclusion

Several articles indicate facilitation of surgery after IVB injection. This is mainly related to the decreased intraoperative bleeding which leads to less exchange of instruments and shorter operative time. Also, IVB pretreatment may decrease the rate of postoperative hemorrhage and shorten the resorption time when it occurs.

Preoperative IVB injection may be associated with complications, the most notable being occurrence or progression of TRD in eyes with significant glial-vascular proliferation. This may be avoided by decreasing the interval between injection and vitrectomy (maybe within 1-5 days). Also, caution should be exercised when injecting IVB in eyes with a florid retinopathy with a predominance of plethoric neovascular channels over the fibrous component, ring-shaped fibrovascular membrane

formation and absence of previous panretinal photocoagulation.

In cases with recurrent postoperative vitreous hemorrhage IVB injection may help to stabilize the eye and prevent further hemorrhage. In severely ischemic eyes in which iris neovascularization and neovascular glaucoma develop after vitrectomy, complete endolaser photocoagulation and silicone tamponade, intrasilicone injection seems to be the only treatment option that has resulted in regression of iris neovascularization and neovascular glaucoma. This treatment has also been successful in recurrent episodes of neovascularization.

To be able to make a proper recommendation for a therapy, the level of evidence should be assessed. Eleven studies in this article were case reports and prospective and retrospective case series, which are classified as very low and low quality studies considering their limitations.<sup>38</sup> Of the 8 prospective randomized trials evaluated, one study<sup>25</sup> had higher quality than the others, however, none may be classified as high quality study based on their limitations in study design and/or conduction according to the reported data. Considering that no study showed significant negative effect of IVB injection in properly selected eyes, based on the present evidence levels, preoperative IVB injection is probably a useful adjunct to diabetic vitrectomy.

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