Original Article

Role of Intravitreal Bevacizumab before Pars Plana Vitrectomy in Patients with Vitreous Hemorrhage Due to Proliferative Diabetic Retinopathy

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Purpose: To investigate the role of Bevacizumab as an adjunct to the management of patients with proliferative diabetic retinopathy undergoing pars plana vitrectomy.

Material and Methods: Hundred and eight eyes of 108 patients with proliferative diabetic retinopathy scheduled for surgery were included in the study. They were randomized to vitrectomy with preoperative IVB (group 1) or standard vitrectomy (group 2). Group 1 underwent a single intra-vitreal injection of bevacizumab 1.25 mg /0.05ml one week prior to vitrectomy. Main outcome measures were best corrected visual acuity (BCVA) after surgery, post-operative complications.

Results: Mean age of the patients was 52.07±5.54 years (range 39-67). At 6 months, 40 patients in group 1 had BCVA better than baseline as compared to 24 patients in group 2. In group 1, only one patient had early post-operative vitreous hemorrhage, whereas 22 patients in group 2 had early vitreous hemorrhage.

Conclusion: Pre-operative IVB is helpful in improving BCVA post operatively, reducing the time of surgery, decreasing the incidence of intraoperative and postoperative bleeding and reducing the frequency of rubeosis and hyphaema.

The aim of vitrectomy in proliferative diabetic retinopathy is to re-establish visual acuity through removal of vitreous blood, removal of fibrovascular proliferation causing traction and to stabilize the neovascular process through panretinal endophotocoagulation of ischemic retina.

Intravitreal bevacizumab (IVB) has been shown to effectively reduce rubeosis and retinal neovascularization in proliferative diabetic retinopathy (PDR).[1,2] Also, administration of IVB prior to diabetic vitrectomy may reduce intraoperative bleeding and post-operative complications in patients with tractional retinal detachment (TRD).[3] Recurrent vitreous hemorrhage is a common indication for reoperation. Most of the hemorrhages occur during the first 6 months but may occur years later.[4]

Bevacizumab (Avastin) a full length humanized monoclonal antibody to vascular endothelial growth factor (VEGF), initially approved by the US Food and Drug Administration (FDA) for the treatment for metastatic colorectal cancer, has now been used in age-related macular degeneration and proliferative diabetic retinopathy (PDR).[2,5] It has also been shown to clear the vitreous hemorrhage rapidly and induce regression of retinal neovascularization[6]. This prospective study was conducted to investigate the effect of IVB prior to diabetic vitrectomy and on its postoperative course.

MATERIAL AND METHODS

Hundred and eight of 108 patients were recruited in

the study. The study was approved by the institutional review board. Study duration was one year i.e. from 1st September 2010 to 31st August 2011. The study was conducted at Isra postgraduate institute Hyderabad, Al Ibrahim eye hospital, Karachi and Jinnah Postgraduate Medical Center.

These patients were diagnosed with proliferative diabetic retinopathy (PDR) and were advised to undergo pars plana vitrectomy (PPV). They were randomized into two categories. In group 1, intravitreal bevacizumab (IVB) was injected 5 to 7 days prior to surgery (60 patients) and group 2 underwent standard PPV (48 patients). All treatment options and the off-label use of intravitreal bevacizumab were discussed with the patient; all patients provided written consent. The inclusion criteria were non clearing vitreous hemorrhage of at least one month, tractional retinal detachment (TRD) involving or threatening the macula, and pre-retinal subhyaloid bleeding covering the macula. Preoperative assessment included best-corrected visual acuity (BCVA), funduscopy with 90D lens and B-Scan ultrasonography in 18 patients was used as fundus was not visualized clinically. Four patients had visually significant cataract leading to inability to visualize the fundus thus B-scan ultrasonography was used in such patients. All patients were followed up postoperatively at day 1, day 7, day 14, and then monthly up to 6 months. The main outcome measures were improvement of BCVA after surgery, post-operative complications hyphema and rubeosis and frequency of vitreous hemorrhage. Early postoperative vitreous hemorrhage was taken as vitreous hemorrhage occurring within four weeks after surgery. All cases completed a minimum follow up of 6 months.

The patients in group 1 underwent a single injection of IVB one week prior to vitrectomy. After sterile preparation and draping, 1.25 mg / 0.05 ml bevacizumab (Avastin, Genentech) was injected intravitreally in the operating theatre under topical anesthesia. Topical antibiotic (moxifloxacin) was started a day before the procedure and was continued for 3 days post injection. Best corrected visual acuity (BCVA) and ophthalmic evaluation were done on each visit pre and post operatively.

All surgeries were performed by a single senior vitreo-retina specialist with experience of over 4 years in performing vitrectomies and similar vitreo-retinal surgeries. Postoperative assessment was also done by a single examiner with over 5 years of experience in diagnostics in vitreo-retina. This observer was kept blind about the group of patient being examined in order to prevent examination bias.

Standard 20 gauge 3-port PPV was performed using Alcon Accurus surgical system. Tractional membranes were removed using peeling, segmentation, delamination and en bloc dissection. Pan retinal photocoagulation (PRP) was done at the end of surgery. Internal tamponade used was either gas or silicone oil 5000 cSt.

Around 15 patients were lost (from both the groups) to follow up and thus were not included in the data.

RESULTS

Hundred and eight eyes of 108 patients were included in the study. Mean age of the patients was 52.07 ± 5.54 years (range 39 – 67). There were 64 males and 44 females. Out of 108 eyes, 70 (64.8%) had no tamponade used while in rest of the 38 (35.2%) eyes, silicone oil was used. Post-operative BCVA is shown in (Table I).

Change in BVCA was categorized as improvement, deterioration or no change. Patients in the group 1 had much better visual acuity than patients in group 2. Most of the patients 36(75%) had their BCVA in the range of 6/60 or better compared to group 2 where only 28 (46%) patients had BCVA better than or equal to 6/60. In group 1, 40 (83%) patients had visual improvement while 6 (13%) had no change and only 2 (4%) had worsening of BCVA. On the other hand in group 2, 24 (40%) patients had improvement in BCVA while 32 (53%) had no change and 2 (7%) had worsening of BCVA (Table 2). No significant difference was observed in the frequencies of postoperative rubeosis and hyphema among the groups (Table 4).

In group 1, only 6 (12.5%) patients had vitreous hemorrhage, 4 of them had it in later stage. In group 2, 40 (60%) patients had vitreous hemorrhage. Out of these, 22 had it in early post-operative period. The difference in both groups was statistically significant with p value of 0.0021, using independent t test.

DISCUSSION

In our study, patients in the group 1, who had IVB before PPV had much better post-operative visual

acuity than patients in group 2 who had had standard PPV alone. This is comparable to the study by El-Batarny where vision improved in 87% in IVT with PPV group and 80% in standard PPV group.[7] Similarly in another study by Ahmadieh, BCVA was better in the IVB group at 1 month compared with the control group (P<0.004).[8]

Table 1: Post op BCVA in both groups.

	6/6 - 6/618	6/24 - 6/6/60	FC
Group 1	6	36	4
Group 2	0	22	28

Table 2: Comparison of BCVA improvement among the groups.

	Group 1	Group 2
Improved BCVA	40	24
Same BCVA	6	32
Worse BCVA	2	4

Table 3: Frequencies of vitreous hemorrhage among the groups.

	No VIT HG	Early Vitreous HG	Late Vitreous HG
Group 1	42	2	4
Group 2	20	22	18

Table 4: Frequencies of Hyphaema and rubeosis among groups.

	Rubeosis	Hyphaema		Rubeosis
	No	Yes		
Group 1	42	6	Group 1	42
Group 2	46	14	Group 2	46

The incidence of early postoperative vitreous hemorrhage was very low in group 1 where only 6 patients had vitreous hemorrhage. In the other group, 40 patients had vitreous hemorrhage, out of these 22 had it in early post-operative period. It has been shown in a number of studies that IVB may reduce the incidence of intraoperative and postoperative hemorrhage in diabetic vitrectomy.[3,9-11]

It is usually difficult to determine the source of early postoperative vitreous hemorrhage. Surgeons believe that dissected fibrovascular membranes are the source of bleeding which typically bleed within one week of surgery.[12] In our Avastin-treated group, only 6 cases of postoperative bleeding were noticed.

IVB was given only once in group 1 patients at least 7 days before surgery to give enough time to had its effects on high levels of VEGF. Exact mechanism of how it reduces the re-bleeding after surgery is not clear. Furthermore, IVB prior to surgery significantly reduced the duration of surgery. Easier dissection due to the absence of intraoperative bleeding and clear view seem to be the reasons for the reduction in the operating time.

Fewer cases in Avastin group had postoperative rubeosis or hyphaema. El-Batarny also reported a similar finding[7]. Retinal ischemia leads to an increased production of intravitreal VEGF, while inhibition of VEGF activity via IVB decreases VEGF levels and inhibits retinal and iris neovascularisation.[13,14]

CONCLUSION

Intravitreal Bevacizumab reduces retinal neovascularization,[2] thus resulting in better visual acuity postoperatively and reduction in intra and post operative complications when it is used preoperatively in pars plana vitrectomy surgery in patients with proliferative diabetic retinopathy. More studies with adequate sample size are required to confirm this effect.

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