JKAU: Med. Sci., **Vol. 18** No. 3, pp: 81-94 (2011 A.D. / 1432 A.H.)
DOI: 10.4197/Med. 18-3.6

Pre-Operative Intravitreal Bevacizumab (Avastin®) Injection before Diabetic Vitrectomy

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Abstract. Evaluate the effect of intravitreal Avastin® prior to diabetic vitrectomy surgery and assess outcomes on OR time and inter-op block as major advantages. At King Faisal Specialist Hospital and King Abdulaziz University Hospital both in Jeddah, Saudi Arabia plus in UK tertiary care health facilities, 20 eyes underwent diabetic vitrectomy in June 2008 to June 2009; included and randomized to a standard vitrectomy (group 1/ control) or with preoperative Avastin® (group 2/ study). Avastin® was injected 7-14 days preoperative for surgery; main outcomes were surgery feasibility and postoperative complications. Follow-up ranged between 6 and 12 months. A significant reduction of mean surgical time, bleeding frequency and diathermy were noted in group 2 compared to group 1. Gas or air was used in 80% of patients (group 2), while silicone oil 60% (group 1). Postoperative visual acuity improvement was highly significant in both groups. Primary anatomical attachment was achieved in 90.3% (group 2) and 86.6% (group 1). Rate of subsequent surgeries and persistent cataract were higher in group 1. Postoperative bleeding was reported in 26.6% in group 1 and none in group 2 (none related to Avastin® injection or progression of traction). Preoperative Avastin® successfully achieved the goal in diabetic vitrectomy surgery.

Keywords: Intravitreal bevacizumab, Diabetic vitrectomy, Vascular endothelial growth factor, Vitreous hemorrhage.

Introduction

The first goal of diabetic vitrectomy is to restore vision. Surgical objectives to achieve this goal are thorough removal of vitreous blood,

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Accepted for publication: 25 April 2011. Received: 04 April 2011.

and reattachment of the macula. Secondly and most importantly, to stabilize the diabetic neovascular process, thereby, producing long – term anatomic and visual success. The basic surgical objectives are the removal of the vitreous scaffold, removal of the surface fibrovascular proliferation and endophotocoagulation of the ischemic retina. Eyes in which these surgical objectives were achieved and which have a good 6-month outcome tend to remain stable for many years[1-3]. Tractional retinal detachment (TRD) and non-resolving vitreous hemorrhage are common indications for diabetic vitrectomy[3]. Perioperative intraocular hemorrhage represents a serious event during diabetic vitrectomy. Extensive hemorrhage may prevent the successful conclusion of surgery. The removal of clotted blood may not only extend a preexisting retinal break, but also may create new retinal breaks[4]. The most common indication for reoperation after diabetic vitrectomy is recurrent of vitreous hemorrhage. Approximately 60% of eyes develop recurrent vitreous hemorrhage at sometime in the postoperative period[3,5-6]. Hemorrhage occurs within the first few days after surgery, though, it may occur months (two thirds occur during the first 6 months[7]) or years later. Various medications and surgical techniques have been utilized to prevent vitreous hemorrhage. Several interventions successfully have been reported in preventing hemorrhage in the first few days after surgery. However, the percentage of cases with significant hemorrhage is 2-4 weeks after surgery has not been changed by any of these approaches. Such interventions included intravenous aminocaproic acid[8], layering of sodium hyaluronate on areas of severed fibrovascular proliferation[6], intraocular injection of thrombin[9], and endolaser photocoagulation[5]. Air-fluid exchange has not been shown to have long term beneficial effects[5].

Bevacizumab (Avastin®, Genentech Inc., San Francisco, CA) a full length humanized monoclonal antibody to vascular endothelial growth factor (VEGF) was approved by the US Food and Drug Administration (FDA) for the treatment of metastatic colorectal cáncer[10]. Reports on the intravitreal injection of Avastin® (IVA) showed promise for targeting VEGF – implicated intraocular neovascularization seen in age – related macular degeneration[11] and proliferative diabetic retinopathy (PDR)[12]. Avastin® has been shown to enhance the clearance of vitreous hemorrhage and induce involution of retinal neovascularization[12-14] and

the anterior segment neovascularization with no reported serious complications[13,15-17]

This prospective comparative randomized study was constructed to study the effect of preoperative intravitreal injection of bevacizumab on the procedure of diabetic vitrectomy as well as on its postoperative course.

Methods

Twenty patients at King Faisal Specialist Hospital and King Abdulaziz University Hospital both in Jeddah, Saudi Arabia and UK tertiary care health facilities were studied with PDR undergoing pars plana vitrectomy (PPV) were randomly selected by diagnosis into 2 groups; Group 1 undergoing PPV (10 patients) and Group 2 undergoing PPV with preoperative IVA (10 patients) (Table 1). Cases of both groups were matched as much as possible according to surgical indication and preoperative visual acuity. In Group 2, bevacizumab was injected 7 to 14 days preoperatively owing to the arrangement and clearance for surgery.

The admission criteria were TRD involving or threatening the macula; TRD plus vitreous hemorrhage, non-clearing vitreous hemorrhage of at least 3 months and massive pre-retinal subhyaloid bleeding covering the posterior pole. Full preoperative and postoperative evaluation included best – corrected visual acuity (VA), fundus biomicroscopy, gonioscopy and ultrasonography if the fundus could not be seen. All patients were examined postoperatively on the 1st day, 7th day, on 2nd week, 1 month, and thereafter, monthly up to the end of the follow-up. The main outcome measures were based on BCVA together with the feasibility of surgery and postoperative complications. Feasibility of surgery was evaluated through recording the time of surgery, frequency of intraoperative bleeding, frequency of the use of endodiathermy, use of perfluorocarbon liquid (PFCL), and the use of silicone oil tamponade. The time of surgery was calculated as the time from the entry of the probes in the vitreous cavity till the closure of the vitrectomy ports. This time was calculated by revision of the video recordings of surgeries. Additional procedures as elective phacoemulsification – surgery as well as periods of time wasted outside the globe, such as during exchange of the infusion bottle or getting a new light probe were excluded from the time of surgery. The actual surgical time was calculated by adding the time periods during which the

instruments were inside the globe through strict revision of the video

Table 1. Intraoperative and postoperative data and postoperative data.

	Group 1 PPV	Group 2 Avastin + PPV	P Value (w)	P Value (Chi)
Bleeding frequency (times/surgery)				
mean (SD)/(range)	6.8 (1.5)/(4-9)	1.9 (1.1)/(0-4)	< 0.0001	
Diathermy frequency (times/surgery)				
mean (SD)/(range	4.6 (1.2)/(2-6)	0.27 (0.46)/(0-1)	< 0.0001	
Surgical time (min)				
mean (SD)/(range)	93.3 (11.6)/(10-100)	61.6 (14.5)/(40-90)	< 0.0001	
PFCL use, n (%)	8 (53.3)	3 (20)		
Relaxing retinotomy, n (%)	4 (26.6)	2 (13.3)		
Endotamponade, n (%)				
20% Sf6	6 (40)	9 (60)		
Air	0	3 (20)		
Silicone Oil	9 (60)	3 (20)		
VA pre surgery				
mean (+ lines)/(range)	0.016 (6.2)/(HM – 0.1)	0.01(7.3)/(HM -0.1)	P2 < 0.001	
VA post surgery (final)				p = 0.52
mean (+ lines)/(range	0.12 (6.7)/(HM -0.5)	0.18 (6.8)/(HM -0.6)	P1 = 0.003	
VA change, n (%)				
Better	12 (80)	13 (86.6)		
Same	2 (13.3)	2 (13.3)		
Worse	1 (6.7)	0		
Primary attachment, n (%)	13 (86.6)	14 (90.3)		
Subsequent surgeries, n (%)				
cataract + oil removal	7 (46.7)	3 (20)		
Re – PPV	2 (13.3)	1 (6.7)		
Postoperative complications				
Cataract, progressive	7 (46.7)	4 (26.6)		
Cataract, gas – induced	2 (13.3)	3 (20)		
Postoperative bleeding	4 (26.6)	0		
Rubeosis	1 (6.7)	0		
Optic pallor	0	1 (6.7)		
Corneal erosions	5 (33.3)	2 (13.3)		

Abbreviations: PPV= parsplana vitrectomy; VA, best corrected visual acuity; ww.Wilcoxon two-sample test; Chi, Chi square test; PI, preoperative versus final VA in group 1; p2, preoperative versus final Vain group 2; P, p value, visual change between the two groups; SD, standard deviation; min, minutes; PFCL, perfluorocarbon liquid

tapes. The decision to use gas air mixture or air or silicone oil was taken intraoperatively. The rationales for using silicone oil were multiple breaks and highly active retinal neovascularization, with significant intraoperative bleeding predictive of postoperative hemorrhage. Postoperative complications including corneal erosions, recurrent vitreous hemorrhage, reproliferation, cataract, rubeosis, neovascular

glaucoma, retinal detachment, were recorded. Complications related to IVA including increase of traction and any systemic side effects were also recorded. All cases completed a minimum follow up of 6 months.

Bevacizumab Injection

Injection of Bevacizumab was administered (no approval by ethical committee was required as the use of Avastin® is a common practice world-wide); 1.25 mg in 0.05 ml bevacizumab (Avastin®; Genentech) was injected intravitreally under complete sterile preparation in the OPD in the usual sterile method, using topical anesthesia[18]; with iodine, povidine-iodine prepping. Prophylactic topical antibiotic (Oflox) was given for 3 – 5 days post-injection. The patients were seen the next day post-op to rule out endophthalmitis.

PPV

Standard 3 – port PPV utilizing Alcon Accurus surgical system was used. All surgeries were performed by the same surgeon. Preretinal fibrovascular membranes were removed using different techniques including membrane peeling, segmentation, delamination and en-bloc dissection. High speed 20 gauge cutters, up to 2500 cuts/minute were used to cut membranes very close to the retina. PFCL was used to stabilize the retina during membrane dissection whenever was required. Complete panretinal photocoagulation (PRP) was done at the end of the surgery. No internal limiting membrane peeling was done in any of the surgeries. The internal tamponade used was decided intraoperatively, either air, Sf6/air mixture 20% or by silicone oil.

Statistical Analysis

Visual acuity was measured using Snellen's chart and was converted to logarithm of the minimum angle of resolution (logMAR) for calculation of the means. Values were expressed as mean ± standard deviation. Lines of vision lost or gained were calculated as Snellen's lines of vision (*via* logMAR). The Wilcoxon signed-rank test was used for continuous variables as age and Chi-square test for categorical variables; $p < 0.05$ was considered statistically significant. The software used was Stata version 6.0 (Stata Corp, College Station, TX, USA)[19].

Results

Group 1 – PPV

Preoperative Data

The age of the patients ranged between 24 and 65 years with a mean of 46 ± 12 years. All cases, except 1, had previous PRP treatment. Mean preoperative visual acuity was 0.016 ± 6.2 lines (mean logMAR 1.81 ± 0.62) (range between HM and 0.1). 4 (40%) cases had visual acuity of 0.05 or better. Cataract requiring phacoemulsification with lens implant surgery was done in 2 cases.

Intraoperative Data

The mean surgical time was 93.3 ± 11.6 min (range 70 to 110 min). Mean bleeding frequency was 6.8 ± 1.5 times/case (range between 4 and 9 bleeding attacks/case). Intraoperative bleeding was encountered in all cases. Diathermy was used in all cases with a frequency of 4.6 ± 1.2 times/case (range 2 to 6 times). Dissection under PFCL was used in 5 (50%) cases. Iatrogenic breaks were noted in 5 (50%) cases. Regarding intraoperative tamponade, gas was used in 2 (20%) cases and silicone oil in 6 (60%) cases. The use of silicone was related to multiple breaks and active bleeding neovascularization.

Postoperative Data

The mean follow up period was 8.7 ± 3.04 months (range 6 – 12 months). Anatomical attachment was achieved in 8 out of 10 cases (80%); 2 cases (20%) detached due to reproliferation. Final visual acuity showed improvement in 8 cases (80%), stabilized in 1 case (10%) and deteriorated in 1 case (10%). The mean final visual acuity reached 0.12 + 6.7 lines (mean logMAR 0.91 ± 0.67) (range HM – 0.5). This improvement of mean visual acuity was statistically significant ($p1$ = 0.003).

Postoperative Complications

Persistent cataract was noted in 6 (60%) cases for which all were silicone oil cases. Two (20%) cases developed gas induced cataract which cleared during the first week. Corneal erosions were observed in 1 (10%) case in the early postoperative period. Postoperative bleeding was noted in 2 (20%) eyes during the first 3 postoperative weeks. All cases

cleared spontaneously within 3 – 6 weeks without treatment. Rubeosis iridis was noted in 1 (10%) case and was associated with peripheral detachment in the lower retina under silicone oil. Two cases with re-detachment underwent re-PPV with silicone oil injection or re-injection.

Group 2 – PPV + Bevacizumab

Preoperative Data

The age of the patients ranged between 23 and 57 years with a mean of 44 ± 11. 2 cases had DM type 1 and 8 had type 2. All cases except 2 had some degree of laser treatment during the course of the disease. Mean preoperative visual acuity was ± 7.3 lines (mean logMAR 1.99 ± 0.73), (range between HM and 0.1). Five (50%) cases had visual acuity of 0.05 or better. Cataract surgery was done in 3 cases. There was evident regression of retinal neovascularization with no significant deterioration of traction between bevacizumab injection and PPV in cases of which the retina could be clinically visualized.

Intraoperative Data

The mean surgical time was 45.6 ± 14.5 minutes (range 30 min). Mean bleeding frequency was 1.9 ± 1.1 times/case (range between 0 and 4 bleeding attacks/case). In 3 cases, there was no bleeding at all. Diathermy was used only in 2 cases with the mean frequency of 0.3 ± 0.46 times /case (range 0 to 1 times/case). Dissection under PFCL was used in 3 (30%) cases. Iatrogenic breaks were reported in 3 (30%) cases. Regarding endotamponade, gas was used in 3 (30%) cases and silicone oil was used in 5 (50%) cases. The use of silicone was related to multiple breaks.

Postoperative Data

The mean follow up period was 9 ± 3.2 months (range 6 – 12 months). Anatomical attachment was achieved in 9 (90%) of 10 cases; 1 case detached due to reproliferation. Final visual acuity showed improvement in 8 (80%) cases and no changes in 2 (20%) cases. The mean final visual acuity reached 0.18 ± 6.8 line (mean logMAR 0.75 ± 0.68) (range between HM and 0.6). The difference in the mean visual acuity between the 2 groups was not statistically significant (p + 0.52). Postoperative complications were persistent cataract, thus, reported in 3 (30%) cases. Corneal erosion was observed in 1 (10%) case in the early

postoperative period. None of the cases developed postoperative bleeding or rubeosis. Hence, optic nerve pallor was reported in 1 case (Fig. 1). The comparative intraoperative and postoperative findings of both groups were summarized in Table 1.

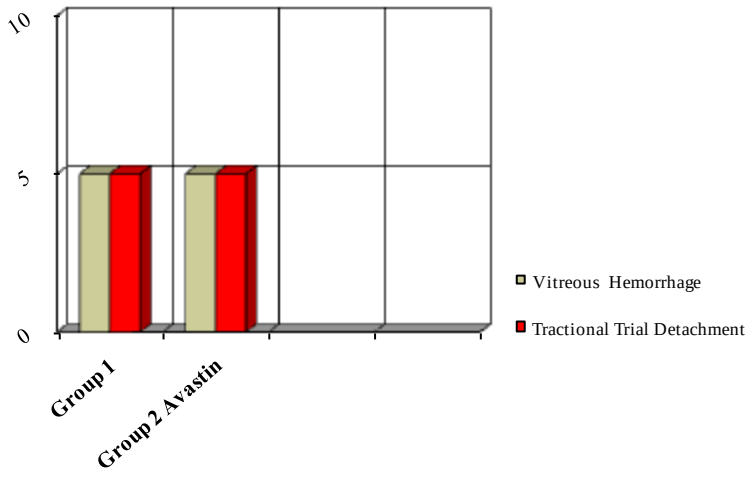

Fig. 1. No. of patients in each group in the study and the indication for performing vitrectomy.

Discussion

Pharmacological blockage of VEGF, postulated to be the factor which is primarily responsible for retinal angiogenesis and vascular permeability has been investigated extensively[20]. VEGF has been shown to contribute significantly to proliferative diabetic retinopathy. Retinal ischemia leads to an increased production of intravitreal VEGF by pigment epithelial cells, pericytes and endothelial cells. Although, inhibition of VEGF activity *via* successful panretinal photocoagulation decreases VEGF levels and inhibits retinal neovascularization[21].

This study was done in a tertiary care center; intravitreal bevacizumab was injected in an effort to quiet down the fibrovascular proliferation before vitrectomy, making surgery easier. In the current study, there was marked reduction of intraoperative bleeding in group 2 which was reflected in minimal need to use the endodiathermy. The nearly absence of intraoperative bleeding in Avastin® – treated cases can explain the easier dissection of membranes in that group. It is sometimes very difficult to peel clotted blood tightly; adherent to the retinal surface

which had led to the higher incidence of retinal iatrogenic breaks in group 1. Lee and Abrams[4] reported that the removal of hemorrhage not only may extend a preexisting retinal break, but also may create new retinal breaks; therefore hemorrhage should be avoided whenever possible. The absence of intraoperative bleeding with evident involution of neovascular complex explains the higher incidence of using gas and air in group 2, in contrast to higher incidence of silicone oil in group 1. Approximately, 60% of eyes develop recurrent vitreous hemorrhage sometime in the postoperative period. Hemorrhage is usually within the first few days after surgery[5,7]. Two thirds of all hemorrhages occur within the first 6 months[4,7]. Novak and colleagues[22] reported that vitreous hemorrhage was present on the first postoperative day in (63%) of eyes. This early hemorrhage cleared in an average of 9.1 weeks in phakic eyes and 3.4 weeks in aphakic eyes.

In early postoperative periods, the source of hemorrhage is often difficult to determine. However, most of the surgeons believe that severed fibrovascular membranes are the usual source of bleeding which usually occurs within 1st week of surgery[3-4]. In the Avastin®-treated cases, no postoperative bleeding were reported in all cases. A single dose of bevacizumab was found to provide the complete VEGF blockade for a minimum of 4 weeks[23], thus providing a haemostatic effect extending beyond the absorption of the gas. This might have prevented recurrence of bleeding in the early postoperative period in group 2 giving a chance for full PRP to induce persistent neovascular regression. In group 1, on the other hand, 2 cases out of 10 cases were treated with gas tamponade (20%) and developed early postoperative bleeding. However, in the remaining cases, the long – term silicone tamponade was the main factor in preventing bleeding in the early postoperative period. The time of surgery was significantly reduced in Avastin® group compared to group 1. In a study done by Rizzo and colleagues[24], the mean surgical time was reduced from 83 min to 57 min after preoperative injection of Avastin® as well as the reduction of frequency of intraoperative bleeding and the use of endodiathermy. Good visualization due to the absence of significant intraoperative bleeding and easier dissection seem to be the reason for the reduction in the surgical time. Scholda and colleagues[25], reported an extensive obliteration of neovascularization with only little intraoperative bleeding during surgery after intravitreal Avastin®. However, Chen and Park[14], after injecting Avastin® in a

case of TRD 1 week before surgery, reported that most epicenters of neovascularization peeled with blunt dissection, suggesting that the recently active neovascular complex had regressed and fibrosed.

In the Avastin® – treated cases, no increase in the extent of tractional on the retina was observed. This is because of the short duration between intravitreal injection and surgery which did not exceed 1 week. Scholda and colleagues[25] reported on 10 cases with advanced PDR treated with Avastin® 2-3 weeks prior to surgery, the authors reported marked contraction of the remaining fibrous tissue. Arevalo and colleagues[26], reported that time from injection to progress or development of TRD had a mean of 13 days (range: 3 to 31 days). The authors reported development or progression of TRD in 11 (5.2%) out of 211 eyes after IVA.

The anatomical and visual results seem comparative in both groups. The vision improved in 80% in group 2 and 80% in group 1 with 20% achieving VA of 20/50 or better in both groups. Improved vision after vitrectomy is now reported for 60% - 80% of eyes with traction macular detachments managed with membrane dissection and PPV. Approximately, 20% of patients achieve vision of at least 20/40[3]. In the Diabetic Retinopathy Vitrectomy Study, patients with active proliferation and good vision preoperatively attained vision of 20/40 or better in 41% eyes postoperatively (DRVS 1988). Thompson and colleagues[27] reported poor initial visual acuity as a predictive factor of poor visual prognosis.

Good anatomical results were achieved in both groups, however, in group 2 this was achieved with short term endotamponade (gas or air) in 30% of cases with less frequency of second surgery, while in group 1, silicone oil use was 60% with subsequent higher rate of re-do surgery; silicone oil + cataract surgery. The choice of silicone oil in this group was strongly related to bleeding tendency which was minimized in group 2 by the IVA. Riedel and colleagues[28] recommended that oil use be reserved for cases with advanced PDR or intractable PVR. Silicone oil provides the longest term tamponade, and has the additional benefit of noncritical posturing. IOP elevation is rarely a problem in the early postoperative period[29]. Disadvantages include the certainty of cataract formation and the fact that at some point, the oil must be removed if visual rehabilitation is to be accomplished[27]. Pearson and colleagues[30]

studied the effect of silicone oil removal following diabetic vitrectomy and concluded that the eventual final visual outcome in these eyes was encouraging in that once cataract and oil were removed; most eyes recovered the acuity achieved soon after initial vitrectomy.

Good anatomical results in both groups can be ascribed to the improvement in vitrectomy equipment. The use of the high speed cutter effect enables shaving of membranes very close to the retina with minimal trauma. Although, not frequently done, anterior peripheral retinal cryotherapy combined with cryotherapy of sclerotomy sites might be helpful adjunct procedures in diabetic vitrectomy for inhibition of fibrovascular ingrowth and in the prevention of recurrent vitreous hemorrhage[31]. Mason and colleagues[32] reported that using cryotherapy around sclerotomy sites and endolaser in a near-confluent pattern helps to quell fibrovascular in-growth and subsequent hemorrhage.

In conclusion, preoperative IVA was successful in achieving the surgical and anatomical goals by reducing the time of surgery, reducing the intraoperative and postoperative bleeding. The combination of therapies and interventions as they improve and evolve offers the potential to revolutionize the approach to the complications of diabetic eye disease. Despite of the few sample study cases, the results in the current study are in agreement with international practice. Hence, more studies in a larger scale are recommended as to properly asses and reduce the impediment of eye disease in diabetic patients.

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استخدام حقن مادة الأفاستين داخل العين كمساعد قبل عملية إزالة الجسم الزجاجي والنزيف في مرضى الشبكية السكري

سعدعبدالله وهيب

قسم العيون، كلية الطب، جامعة الملك عبدالعزيز

جدة – المملكة العربية السعودية

المستخلص. الهدف من هذه الدراسة هو تقديم تأثير حقن مادة الأفاستين، مادة مضادة لنمو الأوعية الدمويّة الجديدة داخل العين لمرضى الشبكية السكري قبل إجراء عملية سحب النزيف واستئصال الجسم الزجاجي. تم عمل عشرين عملية لعشرين مريض بين يونيو ٢٠٠٨ م إلى ٢٠٠٩م. وقد قسم المرضى إلى مجموعتين، مجموعة (١): أجريت العمليات يوم حقن الأفاستين، ومجموعة (٢): تم حقن الأفاستين ٧–١٤ يومًا قبل العملية، وتمت مقارنة النتائج بين المجموعتين، وتبين أن حقن الأفاستين يساعد على تقليل نسبة النزيف أثناء العملية، وبالتالي نجاح العملية، والوصول إلى نسبة نجاح مرضية، وتقليل احتياج العين إلى عملية أخرى.