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ORIGINAL ARTICLE

Retrospective Review of the Adjunctive Use of Pre-Operative Ranibizumab "LUCENTIS™" in the Surgical Management of Diabetic Retinopathy in a Tertiary Referral Hospital in Malaysia

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ABSTRAK

Satu siri kes retrospektif untuk menyelidik peranan dan keselamatan suntikan pre-operatif faktor *anti-vascular endothelial growth* (anti-VEGF) ranibizumab "LUCENTISTM" untuk pesakit yang mengidap penyakit retinopati diabetes yang perlu menjalani pembedahan vitrektomi telah dijalankan. Siri ini melibatkan dua puluh mata konsekutif dari 16 pesakit yang menerima suntikan tersebut 3 hingga 8 hari (purata 4.4 hari) sebelum vitrektomi untuk retinopati diabetis. Umur pesakit adalah dalam lingkungan 46 hingga 72 tahun (purata 57.7 tahun). Tiada berlaku sebarang komplikasi setempat ataupun sistemik. Indikasi untuk vitrektomi adalah *retinal detachment* (RD) [n=11; 3 kombinasi *tractional* (TRD) - rhegmatogenous RD (RRD), 8 TRD], TRD dengan pendarahan vitreus (VH) (n=3) ,VH (n=8) dan sindrom traksi vitreo-makular (n=1). Kriteria kemasukan ialah semua kes konsekutif yang menjalani vitrektomi yang ulung-ulung kali menerima suntikan anti-VEGF sebelum pembedahan. Tahap penglihatan (VA) sebelum pembedahan ialah 6/36 hingga persepsi cahaya. Semua mata berdarah dengan kadar minima ke sederhana semasa pembedahan. Pendarahan (VH) selepas pembedahan dalam mata yang tiada tamponad ataupun tamponad gas adalah tiada (n=1), minima (n=13) ataupun sederhana (n=1). Tahap pendarahan pada mata berisi minyak silikon pula adalah tiada (n=1), sederhana (n=3) ataupun pendarahan teruk (n=1). Tahap penglihatan (VA) post-operatif adalah tidak berubah (n=2) (10%), lebih baik (n = 14) (70%) ataupun berkurangan (n=4). VA adalah 2/60 atau lebih baik (n=15) hingga tiada persepsi cahaya (n=1). Dua mata mencapai VA sebaik 6/12 (10%). Sepuluh mata (50%) mencapai 6/36 atau lebih baik. Kesimpulannya ialah suntikan pre-operatif intravitreal ranibizumab adalah selamat dan berkesan digunakan untuk pembedahan vitrectomi diabetik dan berupaya mengurangkan pendarahan perioperatif sejurus mampu memulihkan penglihatan pesakit.

Kata kunci: Ranibizumab, adjuvan, retinopati diabetis, vitrektomi

ABSTRACT

A retrospective case series review was conducted to determine the pre-operative role and safety of pre-operative adjunctive anti-vascular endothelial growth factor (anti-

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VEGF) agent ranibizumab "LUCENTISTM" in patients with diabetic retinopathy requiring vitrectomy. The study involved twenty consecutive eyes of sixteen patients (age range: 46-72 years; mean 57.5 years) which received intravitreal injection of 0.5 - 1 mg of ranibizumab 3 to 8 days (mean 4.4 days) prior to vitrectomy for diabetic retinopathy. There were no local or systemic post-injection complications. Indications for vitrectomy were retinal detachment (RD) [n=11; 3 combined tractional (TRD) - rhegmatogenous RD (RRD), 8 TRD], TRD with vitreous haemorrhage (VH) (n=3) ,VH (n=8) and vitreo-macular traction syndrome (n=1). Inclusion criteria include all consecutive eyes of diabetic patients requiring vitrectomy receiving a first pre-operative injection of anti-VEGF. Pre-operative visual acuity (VA) ranged from 6/36 to light perception. All eyes had minimal to moderate intraoperative bleeding. Post-operative VH in eyes without tamponade or gas tamponade was nil (n=1), mild (n=13) or moderate (n=1). Silicone filled eyes had nil (n=1), moderate (n=3) or severe haemorrhages (n=1). Post-operative VA was unchanged (n=2) (10%), improved (n = 14) (70%) or worsened (n=4). VA was 2/60 or better (n=15) to no light perception (n=1). Two eyes achieved 6/12 or better vision (10%). Ten eyes (50%) had 6/36 or better vision. In conclusion, pre-operative intravitreal ranibizumab is safe and useful in diabetic vitrectomy and appears to help with perioperative bleeding leading to improvement in vision.

Key words: Ranibizumab, adjuvant, diabetic retinopathy, vitrectomy

INTRODUCTION

Ranibizumab (Lucentis^{TM}, Genentech Inc, San Francisco, US) is a humanized antigen-binding fragment designed to inhibit all isoforms and active degradation products of vascular endothelial growth factor A (VEGF-A) (Gaudreault et al. 2007). Ranibizumab (Rosenfeld et al. 2006) and other anti-VEGF agents such as bevacizumab (Avastin^{TM}, Genetech Inc, San Francisco) and pegaptanib sodium (Macugen^{TM}) (Gragoudas et al. 2004) have been shown to reduce neovascularisation in age-related macular degeneration (AMD) when injected intra-vitreally.

Diabetic vitrectomy is complicated by poor visualisation by the surgeon as a result of haemorrhage due to active neovascularisation. Post-operative vitreous haemorrhage is a further complication, resulting in decreased visual acuity as a result of bleeding particularly from optic disc neovascularisation, which cannot be directly cauterised.

A number of case series utilizing intraocular injection of bevacizumab, a drug designed for systemic anti-cancer use as an "off-label" adjunct to reduce retinal neovascularisation prior to diabetic vitrectomy have been published (Yeoh et al. 2008). Bevacizumab has been shown to induce rapid regression of retinal and iris neovascularization in proliferative diabetic retinopathy (PDR) (Avery et al. 2006).

Therefore, the aim of our study was to investigate the safety and benefit of giving an intraocular injection of ranibizumab, a drug designed and licensed for intraocular injection for AMD, prior to diabetic vitrectomy to reduce the intraoperative and post-operative bleeding in the eye. There has been no such study to date.

MATERIALS AND METHODS

A retrospective study was performed at the Universiti Kebangsaan Malaysia Medical Centre (UKMMC). The medical records of 16 diabetic patients were reviewed. These eyes received 20 consecutive ranibizumab injections from July

2007 to February 2009 prior to vitrectomy.

All patients were known diabetics diagnosed by a physician and were on treatment with including oral hypoglycaemics and/or insulin injections. Each study eye had known or suspected diabetic retinopathy. Pre-operative intravitreal ranibizumab was considered for all patients who had never received any prior laser photocoagulation or in whom laser photocoagulation could not be completed due to significant areas of retinal detachment. It was also considered for patients with clinically significant macular oedema secondary to vitreo-macular traction. This included patients with vitreous haemorrhage, tractional retinal detachment (TRD) with or without rhegmatogenous component, vitreomacular traction (VMT) and epiretinal membrane (ERM) secondary to known or suspected proliferative diabetic retinopathy (PDR) with active neovascularisation. When the fundus could not be viewed, B scan ultrasonography was used to confirm the diagnosis.

Patients with prior history of cerebrovascular accident (CVA) or known vascular occlusion of any kind were excluded from injection with of ranibizumab. Injection was only scheduled after the routine pre-operative investigations which included blood pressure reading, full blood count, renal profile, fasting blood glucose level, echocardiogram and chest X ray were acceptable for general or local anaesthesia as the injection was considered a commitment towards operation.

Informed consent was obtained from each patient. This included counseling on the risk of infection, cataract and retinal detachment. Each injection was performed in a clean treatment room in the eye clinic outpatient setting according to strict aseptic technique. Anaesthesia for the procedure was topical with guttae proparacaine hydrochloride (Alcaine^{TM}) and subconjunctival anaesthesia with 2% lignocaine (Xylocaine^{TM}). Subsequently, 5% povidone iodine lid scrub and douche was performed prior to sterile draping. All patients received ranibizumab, which was aspirated by the assistant into a new 30G insulin needle after swabbing each bottle cap with 100% alcohol wipe.

Each injection of 0.05 or 0.1 ml of ranibizumab was given 4 mm from the limbus in phakic patients and 3.5 mm in pseudophakic patients while directing the injection into the centre of the vitreous cavity. Five percent iodine was then reinstilled onto the ocular surface. The patient then received guttae ciprofloxacin eyedrops at 2 hourly intervals for one week. They were given instructions on symptoms and signs of endophthalmitis and were reviewed the following day and on the day of admission for surgery.

Demographical data (age, gender and ethnicity) were recorded. Dates of intravitreal injections, volume of drug injected, surgical indications, operation record of intraoperative bleeding and duration of surgery were noted. Three cases in which anti-VEGF had been injected at any time in the past were excluded from further analysis. The pre-operative visual acuity prior to injection and on admission was noted and the post-operative visual acuity was also noted at one week, one month, 3 months, 6 months after the operation and at last review. The clarity of ocular media was noted from the diagrams and comments in the operative notes and this was correlated with the visual acuity.

Post-operative haemorrhage was graded as “nil”, if all retina details were visible; “mild” if any part of the fundus was slightly obscured with blood vessels, optic disc and /or laser marks visible; “moderate” if any part of the fundus was totally obscured and “severe”, if the entire fundus was totally obscured. The fundus under gas was used for assessment in gas-injected eyes. Any complication of the intravitreal injection was noted.

RESULTS

Fourteen eyes of fourteen patients received intravitreal injection of 0.05 (0.5 mg) to 0.1 ml (1mg) of ranibizumab between 3 to 8 days prior to vitrectomy by two surgeons (Table 1). Mean duration of injection prior to surgery was 4.4 days. One patient received 1 mg of ranibizumab. One patient received injection prior to PPV in both eyes. Patient ages ranged from 46 to 72 years with a mean of 57.7 years. There were 5 males and 11 females. Twelve patients were Malay, 3 were Chinese and 1 was Indian. Twelve were right eyes (Table 1).

There were no complications locally or systemically post-injection. Indications for vitrectomy were retinal detachment in 11 eyes of whom 3 were combined TRD and rhegmatogenous RD (RRD) with macula detached and 8 were tractional detachments involving the macula. Three tractional detachments were in combination with vitreous haemorrhage while there were eleven pre-operative vitreous haemorrhages. One eye had vitreo-macular traction syndrome secondary to PDR. One eye had re-bled 3 years after previous vitrectomy for TRD. Pre-operative visual acuity (VA) ranged from 6/36 to perception of light with the majority (19 eyes) with pre-operative vision of 6/60 or worse.

Pars planar vitrectomy (PPV) was performed in all cases under local (n=17) or general anaesthesia (n=3) by 2 surgeons. 20G vitrectomy was performed primarily in 15 cases and 23G in 5 cases depending on instrument availability and surgeon preference. Panretinal laser photocoagulation (PRP) was topped up or given to the ora in all cases. Intraocular tamponade of silicone oil 1300Cs was used in 5 cases and intraocular gas tamponade was used in 7 cases. Of those under gas tamponade, sulphur hexafluoride (SF6) was used in 5 cases, and octafluoropropane (C3F8) in 2 cases (Table 2).

All eyes had minimal to moderate intraoperative bleeding. The amount of intraoperative bleeding did not correlate with duration of injection prior to vitrectomy but more with the age of the patient and activity of neovascularisation. There was no documented case of progression of tractional detachment to RRD during the study period although fibrosis of neovascularisation was consistently observed to various degrees in patients with view of the retina. Mild progression of the TRD not resulting in RRD accompanied fibrosis in 3 observable cases (Table 3).

Post-operative VH in eyes without tamponade or with subtotal gas tamponade ranged from nil (n=1), mild (n=12) to moderate (n=1) with complete clearance 4 to 90 days post-operatively (mean 21 days). There was one case of slightly increased post-operative VH at 1 week, which cleared by 1 month during the study period.

Silicone oil filled eyes had nil (n=1) to moderate localized preretinal haemorrhages behind the oil (n=3) to severe post-operative haemorrhage (n=1), which cleared after an average of 44.8 days including one which took over 3 months to clear with oil pushed into the anterior chamber. We believe the patient's uncontrolled hypertension was responsible for this outcome as haemostasis was achieved at the end of the operation. Two silicone filled eyes had very minimal haemorrhages and clear fundal view. Duration of follow-up ranged from 1 month (n=19) to 14 months with 18 eyes (90%) having 3 or more months of follow-up. There were 2 patients who defaulted follow-up after 1 and 3 months. (Table 3)

In general, post operative VH cleared in mean time of 17.6 days for 23G vitrectomy and 30.1 days (n=10) for 20G vitrectomy (Table 3). VA had either remained unchanged (n=2) (10%),

Table 1: Showing patient demographics.

Eye	Patient	Age (yrs)	Gender	Ethnicity	Duration of Follow-Up (mths)
	Legend:		M-male F-female	1-Malay 2-Chinese 3-Indian	
1	A	55	F	1	6
2	B	46	M	1	14
3	C	57	F	1	1 (defaulted)
4	D	52	F	1	3
5	E	65	M	1	3 (defaulted)
6	F	55	F	1	6
7	G	55	F	1	6
8	H	72	F	2	3
9	I	65	M	2	3
10	J	56	F	1	9
11	J	56	F	1	10
12	K	49	M	3	3
13	L	57	M	1	12
14	L	57	M	1	9
15	M	61	M	1	3
16	M	61	M	1	1.5
17	N	65	F	2	3
18	O	53	M	1	9
19	O	53	M	1	6
20	P	60	F	1	5.5

improved (n = 14) (70%) or worsened (n=4) with best corrected VA at last review ranging from 2/60 or better (n=15) to no perception of light (n=1). Two eyes achieved 6/12 or better vision (10%). Two eyes gained significant vision from hand motions or counting fingers to as much as 6/9 vision. Ten eyes (50%) achieved 6/36 or better vision. Mean gain in visual acuity was 1.8 Snellen lines. However, 60% of 23G eyes gained at least 3 Snellen lines compared to 46% of 20G eyes.

Two eyes (10%) developed retinal detachment post-operatively. One patient developed total retinal detachment one-month post PPV with gas injection. He underwent further operation and retinal reattachment surgery. Another case developed retinal detachment following cataract extraction and silicone oil removal. There was no emergence or exacerbation of rubeosis in the any of the eyes at 6 months postoperatively.

DISCUSSION

Diabetic retinopathy (DR) is the leading cause of blindness among people of working age worldwide, leading to significant loss of quality of life. During the first two decades of disease onset, nearly all Type 1 diabetic patients and over 60% of type 2 diabetics have retinopathy. In the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), 3.6% of younger-onset patients (type 1 diabetes) and 1.6% of older-onset patients (type 2

Table 2: Showing procedures performed on patients in the study.

Eye	Patient	Indication(s)	Volume of Lucentis	Duration prior to Vitrectomy (days)	Operation performed
1	A	1	0.1ml	4	23G PPV/EL
2	B	2,3	0.05 ml	5	20G PPV/MP/EL/SO
3	C	2	0.05 ml	4	20G PPV/MP/EL/SO
4	D	1	0.05 ml	4	PEA/IOL/23G PPV/EL
5	E	2	0.05 ml	4	PEA/IOL/23G PPV/EL/SF6
6	F	2	0.05 ml	3	PEA/IOL/20 G PPV/EL
7	G	1	0.05 ml	4	20G PPV/EL
8	H	1	0.05 ml	4	PEA/IOL/23G PPV
9	I	1,2	0.05 ml	3	23G PPV/MP/EL/Ret/C3F8
10	J	2	0.05 ml	3	20GPPV/EL/SO
11	J	2	0.05 ml	4	20GPPV/EL/C3F8 gas
12	K	2,3	0.05 ml	3	20GTPPV/MP/EL/Cryo/SO
13	L	1	0.05 ml	6	20G PPV/MP/SF6/IVTA
14	L	4	0.05 ml	8	20G PPV/MP/SF6
15	M	2	0.05 ml	6	20G PPV/SO
16	M	1,2,3	0.05 ml	7	PEA/20G PPV/SO
17	N	1,2	0.05 ml	4	PEA/20G PPV/IOL/EL/SF6
18	O	1	0.05 ml	4	20G PPV/MP/SF6
19	O	1	0.05 ml	4	20G PPVMP/EL
20	P	1	0.05 ml	4	20G PPV/EL

1-Vitreous haemorrhage, 2- Tractional retinal detachment (RD), 3-Rhegmatogenous RD, 4-Vitreomacular traction, PPV- Pars planar vitrectomy, PEA/IOL-Phaco-Emulsification + intraocular Lens implant, MP-membrane peeling, EL-endolaser, Cryo-cryotherapy, Ret-retinectomy, SF6-sulphur hexafluoride, C3F8-octafluoropropane, SO-silicone oil

diabetes) were legally blind (Klein et al. 2007).

The standard treatment for proliferative diabetic retinopathy (PDR) is PRP, which ablates large areas of retina in order to reduce hypoxia. However, in progressive vasoproliferative disorders such as diabetes, and when extensive new vessels or vitreous haemorrhage preclude fundus visualization and photocoagulation, pars plana vitrectomy becomes the only possible approach to prevent permanent visual loss.

Approximately 4.5% of patients with PDR require pars plana vitrectomy (Flynn et al. 1992) despite prior PRP to remove vitreous opacities and fibrovascular membranes and relieve vitreous traction with the first goal being to restore vision (The Diabetic Retinopathy Vitrectomy Study Group 1985; The Diabetic Retinopathy Vitrectomy Study Group 1988).

Despite advances in vitreous surgery, in cases of PDR, the main problem during vitrectomy is intraoperative bleeding (Peyman et al. 1976) which could adversely affect surgical outcome (Lee & Abrams 2001). Other complications include retinal detachment because of iatrogenic breaks, early postoperative haemorrhage and neovascular glaucoma related to lens removal (Lee & Abrams 2001).

The usage of intravitreal ranibizumab in our study was able to reduce intraoperative bleeding, an observation comparable to studies by Yang et al. (2008) and Oshima et al. (2008) who conducted studies with another anti-VEGF agent, bevacizumab. Furthermore, the usage of ranibizumab in the setting of 23G vitrectomy appears to halve the duration of post-operative vitreous haemorrhage when compared to 20G vitrectomy. This result is comparable to the experience with bevacizumab when used in diabetic vitrectomy (Yang et al. 2008) supporting a safe and effective role for ranibizumab.

Visual acuity cannot be used alone in the evaluation of outcome following dia

Table 3: Showing results of the interventions.

Eye	Patient	Intra-operative bleeding	Post-operative bleeding	Duration of post-op bleed (days)	Pre-op Visual Acuity (VA)	Final VA	Vision gained (number of Snellen lines)	Complications
1	A	1	1 –with residual inferiorly	17	CF	6/24,6/9,N18	3	Nil
2	B	2	1-preretinal haemorrhage	14	6/36,N36	6/18,6/12,N12	2	RRD (localized)
3	C	1	0	NR	6/60,N36	3/60, 6/60	0	High IOP
4	D	0	1	4	1/60, same	6/24,N12	3	ERM
5	E	1	1	30	6/60 same	3/60, 3/60, n48	-1	ERM (fine)
6	F	1	2	28	CF	6/36,6/18,N36	4	Nil
7	G	2	1 with recur at 1 week	30	HM	6/12,6/9,N6	6	ERM
8	H	2	1	30	CF	6/36,6/18,N12	5	Prolonged epithelialdefect
9	I	1	1	7	6/60, N24	CF	-1	VH & RRD (total)
10	J	1	1 superior	14	CF	6/18+2, N9	4	Cataract
11	J	1	1 under gas	90	CF	6/60, 6/24, n12	3	Cataract
12	K	1	1 preret haem	30	6/60	2/60,N36	-1	Nil
13	L	1	1	21	CF	6/24, N12	3	Nil
14	L	1	0	30	CF	CF	0	Nil
15	M	1	2	14	PL	NPL	-1	Severe post-op haemorrhage with oil in AC
16	M	1	1	30	CF	HM	-1	Nil
17	N	0-1	1	NR	HM	CF	1	Nil
18	O	1	1	NR	2/60	6/60, 6/36, N24	2	Cataract
19	O	1	1	NR	4/60,N48	6/25, 6/18, N12	4	Nil
20	P	0	1	NR	HM	6/24, 6/24, N36	4	Nil

0-nil, 1-mild, 2-moderate, 3-severe, Snellen VA 6/ ; CF- counting fingers; HM – hand motions; PL-light perception; NPL-no light perception; N –near vision chart; RRD-rhegmatogenous RD; IOP-intraocular pressure; ERM-Epiretinal membrane; AC- anterior chamber

betic vitrectomy due to the compounding factors of cataract, macular oedema and macular ischaemia. Visual acuity in our study group improved in up to 50% of eyes with a mean gain of 1.8 Snellen lines. Interestingly, the proportion of 23G vitrectomy eyes gaining 3 lines of vision was higher than eyes undergoing 20G vitrectomy at final review. This finding is similar to that of Oshima et al. (2008) who found a higher proportion of eyes gaining 3 lines of vision with smaller incision vitrectomy reflecting a clear advantage of the usage of 23G vitrectomy in combination with anti-VEGF.

Vascular endothelial growth factors (VEGF), increase vessel permeability by increasing the phosphorylation of tight junction proteins. VEGF levels in the retina and vitreous of human eyes correlate with severity of PDR (Aiello et al. 1994).

Ranibizumab "LucentisTM" (49 kDa) has a terminal half-life of 2.9 days in the ocular compartments with low systemic exposure, measuring less than 0.01% of vitreous exposure and is able to penetrate all retinal layers. Increased retinal and vitreous VEGF-A levels were observed in ischaemic retinopathies induced by oxidative damage and hypoxia (Krzystolik et al. 2002). While studies on immortalised bovine retinal endothelial cells (iBREC), show that ranibizumab reverses VEGF-induced cell migration and proliferation (Deissler et al. 2008), it also causes retinal arteriole vasoconstriction. Although ranibizumab is able to reduce bleeding through vasoconstriction (Papadopoulou et al. 2009), the already compromised circulation of the diabetic retina may be further compromised. Hence further studies are required to address this delicate issue and its impact on case selection.

Bevacizumab (AvastinTM) (149kDa) on the other hand, was designed as a chemotherapeutic agent which acts to inhibit tumour angiogenesis such as in cases of metastatic colonic or rectal carcinoma (Ferrara et al. 2004). Bevacizumab is a humanized monoclonal antibody that binds to all isoforms of VEGF and is significantly cheaper than ranibizumab. Off-label usage of intravitreal bevacizumab has been documented in the literature as an effective adjunct for diabetic vitrectomy, in numerous retrospective reviews (Yeoh et al. 2008).

Ranibizumab has a faster clearance rate from the eye and lower systemic absorption than bevacizumab (Gaudreault et al. 2007). Systemic pharmacokinetics from the primate suggest that ranibizumab is cleared up to forty times more rapidly from the serum than bevacizumab. This suggests ranibizumab is a safer alternative particularly in terms of the risk from stroke, which is higher in patients taking anti-VEGF agents. This has potential advantages for diabetics who are already at risk for thromboembolic events due to the associated atherosclerosis and concurrent hypertension and hyperlipidaemia. There were no thromboembolic complications from stroke or acute coronary event in this small series, a reflection of the small, less than 300 times smaller dose used intraocularly than systemic bevacizumab.

Chen & Park (2006) have reported a case of pre-operative bevacizumab use in a 27 year old diabetic with tractional detachment and active vascularisation. They encountered minimal bleeding during segmentation and subsequent delamination of the membranes. We have noted a similar beneficial effect in all our patients with neovascularisation and fibrous proliferation with and without tractional retinal detachment who received ranibizumab prior to vitrectomy.

There are no published data on the duration prior to vitreo-retinal surgery that the intravitreal injection should be given. Most surgeons would recommend that the surgery be undertaken no more than 10-14 days after anti-VEGF injection as the time from injection to TRD is 13 days

(range: 3-31 days). We found that ranibizumab had a beneficial effect when injected from 3 days to 8 days prior to PPV. Bleeding was mild to moderate intraoperatively when given closer to PPV but bleeding could be very little at 8 days or more between 6 to 7 days. As long as this duration is not exceeded, it appears that the activity of the pre-existing neovascularisation was more important than the duration.

Rhegmatogenous retinal detachment occurs in a small percentage of patients after PPV with or without gas tamponade for vitreous hemorrhage or tractional retinal detachment caused by proliferative diabetic retinopathy at a rate of 4.3% (Schrey et al. 2006). Our rate of 10% of retinal detachment may represent a small subgroup of patients in which there was progression of the tractional detachment, for which ranibizumab should be used carefully.

The incidence of endophthalmitis in intravitreal injections of anti-VEGF agents is low at approximately 0.029% (Pilliab et al. 2008). There were no complications from the injection such as uveitis or endophthalmitis in this study.

The limitations of the present study include its retrospective nature and small numbers. There is the ethical dilemma of with-holding preoperative adjunctive treatment with anti-VEGF agents in young diabetics with active neovascular fronds who may be randomised to the control group if the study design was a randomised, controlled trial as the risk of severe intraoperative bleeding is known in this subset of patients. The study adds to the wealth of information on the usefulness of ranibizumab in diabetic vitrectomy of which there are no published data at present. As the role of VEGF inhibitors is not yet established, randomized studies where possible are advocated.

Future improvements in studies of this topic will include prospective studies that incorporate standardized documentation of the degree of visualisation during surgery, records of the bottle height rising time, number of uses of endodiathermy and number of instrument passes for example as well as the degree of reduction in bleeding intraoperatively. This may also include a randomised, controlled trial. Studies comparing ranibizumab with bevacizumab may also yield potential differences and advantages of one over the other.

CONCLUSION

In conclusion, pre-operative intravitreal ranibizumab is safe and useful in diabetic vitrectomy at least comparable in terms of outcome with bevacizumab. It appears to be as helpful as bevacizumab with perioperative bleeding leading to improvement in vision. It has a good safety profile systemically and locally.

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