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The Surgical Outcomes, Complications and Predictive Surgical Factors of Diabetic Retinopathy Vitrectomy in a Large Asian Tertiary Eye Center

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Abstract

Purpose: To evaluate the visual, anatomical outcomes, complications and the predictive preoperative and intraoperative factors of pars plana vitrectomy (PPV) for proliferative diabetic retinopathy (PDR) in a large Asian tertiary eye center

Methods: This is a consecutive retrospective review of 106 eyes that underwent PPV for PDR complications in 2013. The functional success was defined as visual acuity of 20/200 or better while the anatomical success was defined as 360° flat retina without endo-tamponade at one year.

Results: The overall functional and anatomical success was 77.4% and 94.3%, respectively. The common complications were iatrogenic break (14.2%), raised intraocular pressure (IOP) (13.2%), cataract (13.2%) and recurrent vitreous hemorrhage (12.3%). The use of intraoperative triamcinolone (OR: 0.36, p=0.04) and silicone oil (OR: 0.08, p<0.001) were associated with poorer visual success. The iatrogenic breaks occurred more often in 20G PPV than 23G PPV (OR: 5.89, p=0.02) whereas intraoperative silicone oil were associated with postoperative raised IOP (OR: 3.71, p=0.04). The use of bevacizumab was not found to reduce recurrent vitreous hemorrhage (OR: 0.53, 95%CI: 0.11-2.53, p=0.43).

Conclusions: In the era of small gauge vitrectomy, the visual, anatomical outcomes and complication rates of PPV for PDR patients in Singapore had improved significantly, as compared to the Diabetic Retinopathy Vitrectomy Study.

Keywords: Vitrectomy; Diabetic Retinopathy; Surgical Outcome

Introduction

Diabetes is a metabolic disease that can result in numerous macro-vascular and micro-vascular complications, including diabetic retinopathy (DR). Diabetes is increasing in prevalence in Asia and DR is a leading cause of acquired vision loss [1]. A pooled analysis of 22,896 diabetic patients from 35 population-based studies in the U.S., Australia, Europe and Asia (between 1980-2008) showed that the overall prevalence of any DR (in T1DM and T2DM) was 34.6% (95%CI 34.5-34.8), with 7% (6.9-7.0) VTDR [2]. In Singapore, the overall age-standardized prevalence of diabetic retinopathy (DR) was 25.4% (20.1%, 24.8% and 28.9% for Chinese, Malays, and Indians, respectively) [3].

For patients with PDR, the common indications for vitrectomy are persistent vitreous hemorrhage (VH), tractional retinal detachment (TRD) involving the macula, combined tractional and rhegmatogenous retinal detachment (TRRD), vitreomacular traction (VMT) and progressive fibrovascular proliferation [4,5]. Since the Diabetic Retinopathy Vitrectomy Study (DRVS) [6], a few studies have shown that the surgical outcomes of diabetic vitrectomy have improved significantly with the preoperative use of anti-vascular endothelial growth factor (anti-VEGF) and intraoperative use of endolaser and microincision vitrectomy surgery [7,8]. However, there is limited data on the effectiveness of these surgical adjuvants on the outcomes of pars plana vitrectomy (PPV) for complications of PDR patients in Asia.

The purpose of our study is to evaluate the visual, anatomical outcomes, complications of PPV in PDR patients in a large Asian tertiary eye center and assess if preoperative and intraoperative factors affect these outcomes.

Methods

This is a consecutive and retrospective review of all PPV performed between 1st January 2013 and 31st December 2013 for complications secondary to PDR in Singapore National Eye Center (SNEC), the largest tertiary eye center in Singapore. The data was documented by the attending surgeon at the time of surgery and during follow-up and retrospectively collected from the medical records. All patients with complications of PDR who underwent PPV performed by eight retinal surgeons in 2013 were included. The indication for surgery included persistent VH, TRD, combined RRD and TRD, progressive fibrous proliferation, VMT and persistent clinically significant macular edema (CSME) with epiretinal membrane (ERM). Those with previous PPV or less than 12 months follow-up were excluded from the data analysis. This study was conducted in accordance with the Declaration of

Helsinki, with approval from the SingHealth Institutional Review Board.

We collected data including patients' demographics, diabetes history, medication use, indication for PPV, pre-operative best-corrected visual acuity (BCVA), use of pre-operative panretinal photocoagulation (PRP), pre-operative use of anti-VEGF, intra-operative staining adjuvants such as triamcinolone, and 0.15% Trypan Blue/0.025% Billiant Blue G (Membrane Blue-dual, D.O.R.C. International BV, Zuidland, Netherlands), intra-operative endotamponade, intraoperative and postoperative complications. All patients underwent either 20 Gauge (G) PPV or 23 G microincision vitrectomy surgery (MIVS) without the use of chandelier.

Each PPV was performed using high-speed vitrectomy machines (Constellation, Alcon and the Stellaris PC, Bausch and Lombe) with a wide-angle viewing system (Topcon OFISS vitrectomy microscope). For eyes with TRD, the fibrovascular tissue and tractional membranes were removed using segmentation and delamination techniques with intraocular scissors or microvitrector tip, aiming to relieve all traction around the neovascular fronds. In the eyes with VMT, the primary aim was to separate and relieve the vitreomacular adhesion from the underlying macula. Hemostasis was maintained by raising intraocular pressure and endodiathermy. Both intraocular gases [sulfur hexafluoride (SF6), hexafluroethane (C2F6), octafluropropane (C3F8)] as well as silicone oil were the endotamponades used and the decision was made by the surgeon at the time of surgery.

In our study, the functional success was defined as visual acuity (VA) 20/200 or better. We also compared the pre- and post-operative visual mean logarithm of the minimum angle of resolution (logMAR). Anatomical success was defined as 360° flat retina at 12 months without any endo-tamponade. All silicone oil was removed within 12 months of post-operative follow-up.

Postoperative vitreous hemorrhage is defined as any vitreous hemorrhage that occurred within 12 month after operation. Iatrogenic breaks were defined as full thickness breaks in the neurosensory retina created intra-operatively and noted by the surgeon in the medical records. Statistical analysis was performed using the Stata 11.0 (StataCorp, College Statin, TX, USA) with significance set at $p<0.05$ for all analyses. An independent-samples t-test was conducted to compare preoperative versus the postoperative visual outcome and the visual improvement of different diabetic eye diseases. To examine the association of anatomical and functional outcome with various risk factors, generalized estimating equation models were used on eye-specific data and adjusted for age and gender. Descriptive statistics were calculated for all continuous variables.

Results

Patients' demographics and surgical indications

A total of 165 eyes underwent PPV surgery for PDR between 1st January 2013 and 31st December 2013 but only 106 eyes that had month-12 follow up were included in the analysis. Eleven patients had operation performed in both eyes. The mean age and HbA1c were 52 ± 12 years and 8.2 ± 2.1 % respectively. The most common indication for PPV in our study was TRD (52.8%, n=56) followed by VH (38.7%, n=41), VMT (5.7%, n=6), persistent CSME with ERM (1.9%, n=2) and progressive fibrous proliferation (0.9%, n=1) (Table 1).

Diagnosis	Number of eyes (%)
1. Vitreous hemorrhage	41 (38.7%)
2. Tractional retinal detachment (TRD)	
(i) Involving macula	30 (28.3%)
(ii) Threatening macula	5 (4.7%)
(iii) With vitreous hemorrhage	11 (10.4%)
(iv) Combined TRD with rhegmatogenous retinal detachment	10 (9.4%)
3. Progressive Fibrous Proliferation	1 (0.9%)
4. Vitreomacular traction	6 (5.7%)
5. Persistent clinically significant macular edema with epiretinal membrane	2 (1.9%)

Table 1: The indications for pars plana vitrectomy (PPV) for persons with proliferative diabetic retinopathy (PDR).

Types of vitrectomy and intraoperative surgical adjuvants

Majority of the cases were performed using microincision vitrectomy surgery 23G PPV (91.5%, n=97) whereas 9 eyes underwent 20G PPV (Table 2). In addition, 35% (n=37) of eyes had phacoemulsification and intraocular lens implantation performed in combination with the vitrectomy. The intraoperative staining adjuvants were not needed in 63.6% (n=63) of the cases. Most surgeons preferred triamcinolone to 0.15% trypan blue (29.2% vs 10.4%) and in one case both triamcinolone and trypan blue were used. For intraocular tamponade, silicone oil (28.3%, n=30) was the most commonly used agent, followed by sulfur hexafluoride (SF6) (9.4%, n=10), hexafluoroethane (C2F6) (2.8%, n=3) and octafluoropropane (C3F8) (0.9%, n=1). Air alone was used in 6 eyes. 52.8% of the cases (n=56) did not require any tamponade.

Preoperative management		
1. Panretinal photocoagulation	%	n
Yes	85.8%	91
No	14.2%	15
2. Bevacizumab (1.25 mg)		
Yes	23.6%	25
No	76.4%	81
Intraoperative management		
1. Vitrectomy gauge		
i. 23G	91.5%	97
ii. 20G	8.5%	9
2. Combined phaocemulsification and vitrectomy	34.9%	37
3. Staining Adjuvant		
i. None	63.6%	63
ii. Triamcinolone	29.2%	31

iii. Trypan Blue	10.4%	11
iv. Triamcinolone and Trypan Blue	0.9%	1
4. Endotamponade		
i. None	52.8%	56
ii. SF6	9.4%	10
iii. C2F6	2.8%	3
iv. C3F8	0.9%	1
v. Silicone oil	28.3%	30
vi. Air	5.7%	6

Table 2: Preoperative and intraoperative surgical management of proliferative diabetic retinopathy requiring pars plana vitrectomy.

Visual and anatomical outcome

Examining the visual outcomes, 77.4% (n=82) and 31.1% (n=33) achieved BCVA of 20/200 or better and 20/40 or better, respectively (Table 3). The mean logMAR BCVA (standard deviation) improved significantly from 1.30 (0.56) preoperatively to 0.77 (0.74) postoperatively (p<0.001) at month 12. The eyes with vitreous hemorrhage achieved better logMAR VA outcome compared to the TRD group (1.48 to 0.52 versus 1.24 to 0.93, p=0.005). For anatomical success at postoperative month 12, 94.3% (n=100) of the eyes had completely flat retina whereas in 3.8% (n=4) the retina was flat posteriorly with limited detachment peripherally. Two eyes (1.9%, n=2) with TRD had complete re-detachment within 12 months.

Visual outcome (logMAR)	**Preoperative**	**Postoperative**
	Number of eyes (%)	Number of eyes (%)
Overall		
≤ 0.30	3 (2.8%)	33 (31.1%)
>0.30 to ≤ 1.00	37 (34.9%)	49 (46.2%)
>1.00	66 (62.3%)	24 (22.6%)
Vitreous hemorrhage		
≤ 0.30	0 (0%)	16 (39.0%)
>0.30 to ≤ 1.00	11 (26.8%)	20 (48.8%)
>1.00	30 (73.2%)	5 (12.2%)
Tractional retinal detachment		
≤ 0.30	1 (1.8%)	15 (26.8%)
>0.30 to ≤ 1.00	22 (39.3%)	24 (42.9%)
>1.00	33 (58.9%)	17 (30.4%)
logMAR to Snellen's acuity conversion; 0.30=20/40; 1.0=20/200		

Table 3: The visual outcome for overall, vitreous hemorrhage and tractional retinal detachment patients at postoperative month 12.

The types of vitrectomy (20G vs 23G), preoperative use of bevacizumab, preoperative lasers and intraoperative use of membrane blue-dual were not associated with the functional success at month 12 (Table 4). However, multivariate analyses showed that the use of intraoperative triamcinolone (OR: 0.36, 95% CI: 0.14-0.95, p=0.04) and silicone oil (OR: 0.08, 95% CI: 0.03-0.22) were associated with poorer visual outcome, when controlled for age, gender, pre-operative best corrected visual acuity and the abovementioned surgical factors. The visual success for patients who underwent combined phacoemulsification and PPV versus PPV alone were similar (OR: 0.93, 95% CI: 0.37-2.33, p=0.88).

Components	**Functional Success**	
	Odd Ratio (95% CI)	p value
20G vs 23G vitrectomy	0.336 (0.082-1.38)	0.131
Preoperative bevacizumab	0.914 (0.337-2.48)	0.859
Preoperative laser	2.67 (0.879-8.12)	0.083
Intraoperative membrane blue	1.323 (0.292-5.988)	0.716
Combined PPV/phacomulsification vs PPV alone Intraoperative triamcinolone	0.93 (0.37-2.33) 0.371 (0.141-0.975)	0.88 0.044
Intraoperative silicone oil	0.788 (0.028-0.224)	<0.001
Intraoperative triamcinolone*	0.361 (0.137-0.948)	0.039
Intraoperative silicone oil*	0.079 (0.028-0.224)	<0.001
*Multivariate analyses adjusted for age, gender, preoperative best-corrected visual acuity and the parameters in the table, with level of significance at p<0.05.		

Table 4: The preoperative and intraoperative surgical factors related to overall functional success at postoperative month 12.

Pars plana vitrectomy (PPV) complications

Table 5 shows the complications of eyes that underwent PPV for proliferative diabetic retinopathy.

Complications	**% (n)**
Iatrogenic retinal breaks	14.2% [15]
Raised intraocular pressure	13.2% [14]
Cataract	13.2% [14]
Postoperative vitreous hemorrhage	12.3% [13]
Neovascular glaucoma Retinal detachment Endophthalmitis	2.8% [3] 1.9% [2] 0.9% [1]

Table 5: Complications of pars plana vitrectomy performed for eyes with proliferative diabetic retinopathy.

Complications include iatrogenic retinal breaks (14.2%), post-operative cataract formation in phakic eyes (13.2%), and raised IOP (13.2%) and recurrent vitreous hemorrhage (12.3%). Of the patients with raised IOP, 50% (n=7) was transient and settled within one month postoperatively. No hypotony was reported in the case notes. In eyes

with PPV performed for TRD, the rate of iatrogenic retinal breaks was 17.9%. In cases with vitreous hemorrhage, eight eyes (7.5%) required post-operative office-based fluid air exchange for recurrent vitreous hemorrhage.

In a multivariate model adjusting for all surgical factors including preoperative use of bevacizumab or laser photocoagulation, intraoperative use of triamcinolone and membrane blue; 20G vitrectomy was associated with 7.3 times (OR: 7.3; 95%CI: 1.55-34.3, p=0.012) for intraoperative iatrogenic breaks compared with 23G PPV (Table 6). Multivariate analysis also found that patients who had intraoperative silicone oil were 3.7 times more likely to have postoperative raised IOP (OR: 3.7; 95%CI: 1.1-13.1, p=0.04). The use of preoperative bevacizumab was also found to be associated with lower overall anatomical success (retinal re-attachment) in all patients (OR: 0.07, 95%CI: 0.01-0.61, p=0.02). This association was similar in the subgroup of patients treated for TRD (OR: 0.06, 95% CI: 0.01-0.44, p<0.01).

Components	Iatrogenic break		Raised IOP	
	OR (95% CI)	p value	OR (95% CI)	p value
20G vs 23G	5.9 (1.4-25.1)	0.017	0.8 (0.1-7.3)	0.868
Preoperative Bevazicumab	0.9 (0.3-3.1)	0.847	2.2 (0.7-6.8)	0.184
Intraoperative Triamcinolone	1.8 (0.6-5.3)	0.284	1.5 (0.5-4.8)	0.506
Intraoperative trypan blue	2.5 (0.6-11.0)	0.226	0.8 (0.1-5.3)	0.774
Intraoperative silicone oil	9.4 (2.7-32.3)	<0.001	4.6 (1.2-17.9)	0.028
Intraoperative silicone oil*	10.0 (2.8-35.9)	<0.001	3.7 (1.1-13.1)	0.042
IOP: Intraocular pressure; G: gauge; PPV: pars plana vitrectomy *Multivariate analyses adjusted for all variables in the above table, with level of significance at p<0.05.				

Table 6: The preoperative and intraoperative surgical factors related to intraoperative iatrogenic breaks and postoperative raised intraocular pressure (IOP) for pars plana vitrectomy.

	DRVS (n=987)	Yorston (n=174)	DRIVE UK (n=185)	Thompson (n=1007)	Ting (n=108)
Follow up	4 years	8 months	12 months	At least 6 months	12 months
Visual acuity (VA)					
i. ≥ 20/200	63-68%	71.7%	N/A	70%	77%
ii. ≥ 20/40	28-44%	11%	38%	17%	31%
iii. No light perception	19-23%	2%	3%	14%	2%
Anatomical success	63-79%	91%	84%	70%	94%
N/A: Not available.					

Table 7: Comparative visual and anatomical outcome following diabetic vitrectomy for proliferative diabetic retinopathy.

Complications	DRVS (n=317)	Yorston (n=174)	DRIVE UK (n=185)	Kamura (n=760)	Ting (n=108)
1. Iatrogenic breaks	N/A	34.20%	N/A	29%	14.2%
2. Postoperative vitreous hemorrhage	N/A	22%	43.3%	3.6%	12.3%
3. Cataracts	N/A	11.50%	22.6%	N/A	13.2%
4. Raised intraocular pressure	7.7% had neovascular glaucoma	N/A	8.2%	3.9% had neovascular glacuoma	13.2%
5. Retinal detachment	12-21%	3%	10%	3%	1.9%

N/A: Not available

Table 8: Comparative diabetic vitrectomy postoperative complications for proliferative diabetic retinopathy.

Discussion

This study reports the outcomes and complications of diabetic vitrectomy in a large Asian tertiary eye center. Even though it is difficult to compare the results from different centers due to various confounding factors, the visual and anatomical outcomes of our patients compare favorably with some recent published series (Table 7) [9-11]. The overall functional success (VA ≥ 20/200) and anatomical success was 77.4% and 94.3%, respectively. The main indications for PPV in PDR patients were vitreous hemorrhage and tractional retinal detachment. The most common complication was iatrogenic retinal breaks (14.2%), followed by cataract (13.2%), raised IOP (13.2%) and recurrent vitreous hemorrhage (12.3%), which are similar to the other published studies (Table 8). With the advancement of vitrectomy techniques, the surgical outcomes and complication rate have significantly improved since Diabetic Retinopathy Vitrectomy Study was published [12,13].

Vitrectomy for PDR can often be complex and challenging. The rate of recurrent vitreous hemorrhage within one month postoperatively was only 12.3% and this is significantly lower than the previously reported rate [14]. This is likely due to meticulous surgical technique to achieve intraoperative hemostasis with the use of intraoperative manipulation of intraocular pressure, endodiathermy, adequate clearance of vascular traction, and intraocular tamponade. Since this is a retrospective review of medical records, there is a possibility there was unreporting of mild, visually insignificant vitreous hemorrhage.

Some studies have reported on the use of anti-vascular endothelial growth factor (VEGF) in reducing the incidence of postoperative vitreous hemorrhage without having any impact on final postoperative visual outcome [15-17]. In our study, 1.25 mg/0.05 mls of preoperative intravitreal bevacizumab was used between 3 days to 2 weeks before surgery according to surgeon preference. Pre-operative bevacizumab was not shown to have any effect on the incidence of postoperative recurrent vitreous hemorrhage and visual outcome. Given the uncertain benefit and potential risk of pre-operative bevacizumab, it is advisable to limit its use in diabetic vitrectomy surgery unless it is performed in a clinical trial setting. However, the low incidence of recurrent vitreous hemorrhage and the variation in use of preoperative bevacizumab will limit the conclusions that can be made.

Silicone oil is used in complex retinal detachment surgery where longer-term tamponade is required, but it can cause elevated IOP postoperatively between 2.2% to 56% of the cases [18,19]. In the silicone study report 4, IOP could potentially remain persistently high after 36 months in up to 9% of the patients [20]. Raised intraocular pressure may be due to overfill of silicone oil, emulsification of oil in the trabecular meshwork or may be related to other factors such as the angle neovascularization and peripheral anterior synechiae with angle closure. In our study cohort, 15 eyes had elevated IOP postoperatively and of which, 40% (n=6) had silicone oil injected intraoperatively. In multivariate analyses, use of silicone oil was associated with 3.7 times increased risk of raised postoperative IOP within one month (Table 6). It is important to monitor the IOP of these patients postoperatively to avoid further compromise of their visual potential.

In our population, the use of silicone oil was associated with poorer visual outcomes. In our practice, silicone oil was reserved for subjects who require long-term tamponade due to multiple breaks or persistent vitreo-retinal traction. These eyes are those with worse pre-existing disease, with higher incidence of ischemia and severe fibrovascular traction and would be more likely to have poorer outcomes.

The incidence of iatrogenic breaks in our study was 14.2%. Of which, 66.7% of these breaks occurred in eyes undergoing vitrectomy for tractional retinal detachment. Our results were comparable to the rate reported in the previous studies [21-23]. Iatrogenic breaks are more likely to occur intraoperatively during surgery to relieve vitreo-retinal traction and dissect fibrovascular membranes [22]. Our series did not have any entry site iatrogenic breaks related to vitreous traction for both 20G and 23G. In a multivariate analysis, 20G PPV was found to have 7.3 times increased risk of iatrogenic breaks compared to 23G PPV (Table 4). The use of high speed 23G microvitrectomy with a cannulated entry system had been shown to have lower the incidence of retinal breaks, due to reduced vitreous base traction during instrument insertion; improved vitrectomy fluidics and increased cut rate with reduced vitreo-retinal traction [23,24]. Nevertheless, the risk of iatrogenic breaks may be over-estimated due to the limited 20G PPV cases (n=9) and it will be of great value to evaluate this in a larger prospective randomized controlled trial.

The use of bevacizumab has been shown to be associated with increased risk of TRD in PDR [25,26]. To date, none of the studies have shown that it reduces the anatomical success of PDR patients undergoing PPV. In our study, the use of preoperative bevacizumab was associated with lower overall anatomical success (retinal re-attachment) in all patients (OR: 0.07, 95%CI: 0.01-0.61, p=0.02) and in patients with TRD (OR: 0.06, 95%CI: 0.01-0.44, p<0.01). This may be due to preoperative rapid neovascular involution with accelerated retinal fibrosis increasing the complexity of the PPV for TRD patients [25]. It is also possible that those who had been given intravitreal bevacizumab are those with active disease or no prior laser photocoagulation where the surgeon expect to require assistance with hemostasis and this group may be predisposed to worse outcomes due to their disease severity. Nevertheless, these results may be limited by the small sample size of partial or complete retina detachment (n=6) and the non-randomised retrospective nature of this study. A larger randomised trial will be needed to evaluate the true impact of pre-operative bevacizumab use on anatomical success and postoperative vitreous hemorrhage.

Our study is limited by the retrospective nature and the collection of data from medical records. Data can only be determined from the medical records, which may be affected by reporting bias. The surgical techniques, adjuvants and tamponade agents used were determined by the operating surgeon and as a result, in a multi surgeon study, it would be difficult to determine the effect of each intervention and the reason for which it was used.

In conclusion, the visual, anatomical outcomes and complication rates of PPV for PDR in Asian patients compare favorably with previous studies published in the Western world. Patients with silicone

oil need to be monitored regularly for increased IOP which can further compromise their long term visual outcome.

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