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Research Article

Anatomic Outcomes after Surgical Management of Retinal Detachment Associated or not with Diabetic Retinopathy

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Received: March 20, 2018; **Published:** June 20, 2018

Abstract

Purpose: To evaluate anatomical single-operation success rate following vitrectomy in the management of traction/rhegmatogenous retinal detachment (RD) associated with diabetic retinopathy, in comparison with non-diabetic eyes.

Patients and Methods: Retrospective, consecutive case series including all patients who underwent pars plana vitrectomy (PPV) in the management of traction/rhegmatogenous RD associated or not with diabetes, at Monticelli-Paradis Center between 2013-2014. Main outcome measures included primary anatomical success rate defined as rates of retinal reattachment after a single operation. The study included 755 non-diabetic eyes and 38 diabetic eyes, with a minimal follow up of 6 months.

Results: Single-surgery anatomical success (SSAS) was achieved in 611 (80.93%) of non-diabetic eyes with RD and in 34 (89.47%) of diabetic eyes. PPV was shown to assure similar anatomical success rate for RD associated with diabetic retinopathy as for non-diabetic RD (P = 0.952).

Conclusion: Favorable anatomic retinal reattachments in selected patients with traction/rhegmatogenous RD can be achieved similarly for diabetic and non-diabetic eyes, following initial management with PPV.

Keywords: *Retinal Detachment; Pars Plana Vitrectomy (PPV); Single-Surgery Anatomical Success (SSAS); Diabetic Retinopathy*

Diabetic retinopathy (DR) is a leading health concern and a major cause of vision loss. Among 285 million people suffering worldwide from diabetes mellitus (prevalence 6.4%), there are 93 million people with DR, 17 million with proliferative diabetic retinopathy (PDR), 21 million with diabetic macular edema (DME), and 28 million with vision threatening DR [1]. By the year 2030, the number of diabetic people in the age-group 20 - 79 years is estimated to reach 440 million (prevalence 7.7%) [2]. DR is the most frequent inflammatory microvascular complication of diabetes mellitus. DR on exam is characterized by microaneurysms, intraretinal hemorrhages, venous beading, cotton-wool spots, macular edema, neovascularization, retinal ischemia, vitreous hemorrhages, retinal break(s) in association with epiretinal fibrovascular membrane proliferation (FVP) and preretinal scar tissue formation that may lead to tractional and/or retinal detachment [3-6].

PPV surgery is normally indicated to avoid permanent vision loss in PDR, when aberrant vessels often grow into the vitreous, are leaky, prone to hemorrhage, leading to the proliferation of epiretinal fibrovascular membranes (FVMs) and subsequent tractional or combined tractional and rhegmatogenous retinal detachment [7,8].

The objective of this study is to find out if diabetes contributes more or less to retinal re-attachment or has a particular effect on anatomical single-operation success rate.

Patients and Methods

Design

A retrospective comparative case series study was performed on patients who underwent primary 25/23-G PPV for the management or tractional/rhegmatogenous retinal detachment complicating a DR or PDR, versus retinal detachment associated with other non-diabetic cases like High Myopia, Pseudophakic/Phakic/Aphakic eyes, post-traumatic complications, cataract, hemorrhages, AMD and other retinopathies, from January 2013 to December 2014. The main outcome measure for this study was "single surgery anatomical success" (SSAS), defined as 1 operation to anatomically reattach 100% of the retina for a minimum of 6 months duration or until the end of the patient follow-up.

Inclusion and exclusion criterias

Have been included 793 eyes with retinal detachment (38 diabetic eyes, precisely 20 eyes with DR and 18 with proliferative DR (PDR) (Table 1) and 755 non-diabetic eyes) of Monticelli-Paradis Center, independently of the simultaneous presence of other retinal complications like idiopathic or secondary epiretinal membranes, idiopathic or traumatic macular hole, progressive fibrovascular proliferations, vitreous hemorrhage, hematoma, glaucoma. Among the non-diabetic eyes, only 26 had myopia greater than -6,00D, 11 phakic and 79 pseudophakic eyes, 5 eyes had post-traumatic hemorrhages and complications, 249 had cataract at the moment of the surgery, 22 eyes with dry AMD, 6 eyes with other non-proliferative retinopathies like hypertensive retinopathies and retinopathy of maturity). Have been excluded the patients with wet AMD and those having received less than 6 months follow up.

Surgical techniques

All patients underwent a standardized surgical procedure for vitrectomy, receiving a standard 3-port 23- or 25-gauge PPV using a non-contact wide-angle viewing system (Binocular Indirect Ophthalmomicroscope), combined or not with phacoemulsification and intraocular lens implantation under retrobulbar anesthesia. In cases when phacoemulsification was combined with vitrectomy, it was performed before the vitrectomy after the canula insertion. Endolaser photocoagulation was applied either around the retinal tear or 360° to the vitreous base to completely surround all retinal breaks. Any 23 G or 25 G sclerotomy sites that were found to be leaking at the end of the surgery were sutured with 7-0 vicryl suture. In all cases, patients received non-expansile perfluoro-n-octane (C_3F_8) in air (12-16%) for simple RD, sulfur hexafluoride (SF_6) in air (20-26%) for larger RD, or silicone oil (1,000 or 5,000-centistokes) for tamponade. All diabetic patients with PDR received the silicone oil for tamponade.

Data Analysis

All statistical analysis was performed using XLSTAT version 2015. Fisher test and z test (unilateral) were applied for data to respectively compare variances and proportions between the two treatment groups. Kruskal-Wallis and Steel-Dwass-Critchlow-Fligner tests were applied to compare statistical variations in anatomical success rates between the participating doctors. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to compare anatomical success rates. Descriptive statistics with z test (bilateral) were sorted out for age and gender effect on SSAS comparison between patients of diabetic group and those of non-diabetic group, then for age and gender effect on RD recidival in the two groups. Same analysis was made to study the correlation of PDR with RD and with RD recidival amongst the diabetic group.

Anatomical results

793 eyes with retinal detachment were retained according to the selection criterias above. These eyes underwent vitrectomy and included 38 with DR, among which 18 with PDR (Table 1) and 755 non-diabetic eyes. The overall SSAS rate for the 793 eyes with retinal

detachment was 81.34%. For the diabetic eyes, SSAS was 0.8947 (4/38 of re-detachment) versus 0.8092 for non-diabetic eyes (144/755 of re-detachment). Z test confirmed this difference was not significant between the two groups (OR of 2.00; 95% CI [0; 0,171]; P =0.952). No significant predominance of males or females was noticed in both groups (P = 0.428) (Table 2). Baseline demographics including gender did not differ between the two groups (P = 0.43) (Table 2). This observation was also confirmed by the Chi^2 test (P = 0.255).

Diabetic Patients with RD	Gender	Age (Years)	PDR	Previous operations	Pre-op complications	Post-op complications	Recidivity of RD
1	M	74.9	Yes	-	Cataract	-	No
2	M	39.7	No	-	-	-	No
3	M	67.3	Yes	-	DME, ERM	-	No
4	M	28.5	Yes	-	-	-	No
5	M	55.8	Yes	-	ERM, neovascular glaucoma	-	Yes
6	M	78.11	Yes	Cataract	-	-	No
7	M	38.10	No	-	-	-	No
8	M	58.4	Yes	Cataract	-	PKE	No
9	F	25.4	Yes	-	-	-	Yes
10	M	37	Yes	-	-	-	No
11	F	22.11	Yes	-	-	Cataract; RDP of the fellow eye	Yes
12	M	70.7	No	-	-	Cataract	No
13	F	39.8	No	-	-	PDR; hemorrhage	No
14	M	53.9	No	-	hemorrhage	Tearing	Yes
15	F	54	No	-	-	-	No
16	F	64	No	-	-	-	No
17	M	44.2	No	-	Cataract Kidney failure	Neovessels	No
18	M	60.1	No	-	-	Cataract, MEM	No
19	F	56.4	Yes (severe)	-	VMT	-	No
20	F	72.11	No	-	Cataract	-	No
21	F	58.5	No	-	Cataract, OMC, HTO > 40	-	No
22	M	28.9	No	-	Hemorrhage	-	No
23	M	45.10	No	2 PPV	-	Ptyst state, diffuse retinal edema; MER	No
24	F	87.5	No	-	Hyphema	-	Yes
25	M	37.7	Yes	Failed renal and intestinal grafts	Refractory glaucoma; Vitreous hemorrhage; Intestinal hemorrhages	-	No
26	M	54.8	Yes	laser	-	-	No
27	M	74.8	Yes	-	VMT	-	No
28	M	60.2	No	-	Cataract	Cataract	No
29	M	61.1	No	-	Cataract	-	No
30	M	81.6	Yes	VMT	-	-	No
31	M	81.2	No	-	-	-	No
32	M	67.1	Yes	Cataract	HIV	-	No
33	M	63.1	Yes	-	Cataract	-	No
34	M	55.11	Yes	-	-	Strabism	No
35	M	64.6	No	PPV	Cataract, Open MH	-	No
36	M	76.5	No	PPV, cataract, many laser sessions	-	-	No
37	F	64.3	Yes	-	-	-	No
38	M	68.2	No	-	-	-	No

Table 1: *Descriptive data of diabetic patients with RD. DME: Diabetic Macular Edema; ERM: Epiretinal Membrane; MEM: Epimacular Membrane; VMT: Vitreomacular Traction; MH: Macular Hole; HIV: Human Immunodeficiency Virus.*

Interestingly however, the mean age was significantly different between the diabetic and non-diabetic groups, with the diabetic group featuring younger patients: mean age of patients in the diabetic group was 57.189 years whilst that of patients in the non-diabetic group was 69.385 years (95%CI, [0.003; 0.294]; P < 0.0001). Mean age of males and females was significantly lesser among the diabetic group than among the non-diabetic group (58.14 ± 15.651 and 68.568 ± 9.970 years old respectively, for males, with 95%CI, [-16.34; -4.156], P =0.001; 54.526 ± 20.263 and 71.562 ± 10.575 years old respectively, for females with 95%CI, [-29.72; -4.353], P =0.008) (Table 2). Mean age of recidival patients of the diabetic group was 55.543 ± 25.378 years while that of recidival patients of the non-diabetic group was 72.141 ± 9.938, (95% CI [-41.645; 8.449]; P = 0.194) (Table 2).

	Diabetic eyes with RD (n = 38)	Non-diabetic eyes with RD (n = 755)	P (Method)
Mean age ± SD (range), years	57.189 ± 16.770 (22.92; 87.42)	69.385 ± 10.218 (33.33; 94.58)	< 0.0001 (Z)
Mean age of Male	58.14 ± 15.651 (28.42; 81.5)	68,568 ± 9,970 (33.33; 91.17)	0.001 (Z)
Mean age of Female	54.526 ± 20.263 (22.92; 87.42)	71,562± 10,575 (45.17; 94.58)	0.008 (Z)
Mean age recidivals ± SD (range), years	55.543 ± 25.378 (25.33; 87.42)	72.141 ± 9.938 (46.92; 94.58)	0.194 (Z)
Male, n (%)	28 (73.68)	502 (66.49)	0.429 (Z)
Female, n (%)	10 (26.31)	253 (33.51)	0.428 (Z)

Table 2: *Characteristics of Study Patients. Comparison of age and gender in the "diabetic eyes with RD" group and the "non-diabetic eyes with RD group".*

(Z) = test z/test bilatéral

Now, patients with PDR were not shown to have significantly more RD than their fellows diabetic patients (95% CI [0.313; 0.640] P = 0.626). Only 1 patient among the 18 patients with PDR manifested DR recidival after the surgery. PDR was not shown to be correlated with RD recidival (P = 0.823 (Chi^2)). Moreover, among the diabetic patients a significant correlation was demonstrated between the gender and the occurrence of RD (95% CI [0.140; 0.434]; P = 0.002 for males and 95% CI [0.566; 0.860]; P = 0.002 for females (Z test)) but not between the gender and RD recidival (P = 0.255 for males (Chi^2)). Only 2/28 males and 2/10 females had RD recidival after the surgery.

Other data like BCVA, duration of symptoms, axial length, average number of breaks, number of inferior breaks and average clock hours detached were not examined in our study, because we expected no significant effect on the SSAS between the two groups, as vigorously supported by a previous study of Kinori., *et al* [13].

Discussion

Our study shows, like previous observations, that surgical intervention for repair of tractional and/or rhegmatogenous formation of RD is highly associated with retinal reattachment and preserved visual acuity in most diabetic eyes [5-9]. This association has been proved in one study to be especially greater when RD involves the macula in one eye and poor vision in the fellow eye [10]. Significant prognostic factors like preoperative BCVA, vitreoretinal adhesion, extent of RD, intraoperative retinectomy, and silicone oil use, all of which might be interrelated, may account for the final SSAS. Extent of RD is usually known to be correlated with enhanced vitreortinal adhesion; previous intravitreal injection or cataract surgery are also presumed to play a role in provoking RD. Now, although the structural pathogenesis of this disease process is such the abnormal tissue consistently grows always nearly along the posterior vitreous surface, exact features and secondary complications vary solely from case to case. Secondary complications are dependent on the places of origin and amount of fibrovascular proliferation, and on the location and extent of any posterior vitreous separation influencing the configuration of the fibrovascular tissue growth [8]. Intriguingly, Kim., *et al.* demonstrated that FVM-derived cultures had more proliferating cells in diabetes compared to the proliferation rate of non-diabetic cells [6] and that among the 11 angiogenesis-related signaling molecules expressed by

FVMs - including angiogenin (ANG), Ang-1, ET-1, insulin-like growth factor binding proteins 2 and 3 (IGFBP-2 and IGPBP-3), monocyte chemoattractant protein-1 (MCP-1), plasminogen activator inhibitor-1 (PAI-1), pentraxin 3 (PTX-3), pigment epithelium-derived factor (PEDF), TIMP metallopeptidase inhibitor 1 (TIMP-1), and Tsp-1 - diabetes or high glucose triggered a statistically significant decrease in the secretion of Ang-1 and Tsp-1 in PDR, factors that are involved in the stabilization and/or inhibition of angiogenesis while curiously, high levels of Ang1 and Tsp-1 were found in patients with non-proliferative DR when compared to patients with PDR. Overexpression of Ang1 has also been found to block the permeability-inducing effects of VEGF [6]. Those differences in the FVM proliferation rate and expressing levels of proteins leading to aberrant angiogenesis didn't seem to favor further post-operative RD. Indeed, our results have not shown any correlation between PDR and the occurrence of RD (P = 0.626), nor between PDR and the recidival of RD (P = 0.823). Previous studies have reported DR to be a risk factor for the occurrence of RD [14]. Effectively, our study showed patients of the diabetic group developed RD significantly earlier than patients of the non-diabetic group (57.189 years old vs 69.385 years old respectively; P = 0.001 for males and P = 0.008 for females).

Nevertheless, we know some post-operative complications are specifically related to the sutureless vitrectomy. Some factors are theoretically known to be specifically associated with complicated vitreoretinal pathologies such as PDR [11], thus we presumed they practically may enhance susceptibility of diabetic eyes to post-operative complications hens probably facilitating retinal re-detachment. Those risk factors include straight sclerotomy incision, young patients, extensive peripheral vitrectomy, extensive intraocular manipulation, previous vitrectomy and long operation times. However, our study didn't accredit diabetes more vulnerability to post-operative suture-dependent re-detachment compared to other types of complications. Few diabetic eyes in our study may have encountered previous laser treatment. In these cases, when progressive tractional forces derived from active FVP or laser energy, pull on the laser-treated area, they may induce retinal breaks from the recently applied laser spots, resulting in combined RD. However, these procedures were performed with caution, we didn't notice any differential observations with non-previous laser treated patients.

Interestingly, we know diabetic patients have an altered immunity at various levels and may be more susceptible to infection after ocular surgery [11]. Chemokines including CCL2 have been implicated in inflammation of the diabetic retina, including the activation of retina microglia and macrophages that could lead to disruption of the blood-retina barrier thus to intraocular pressure (IOP) [12], yet facilitated by PPV. Unexpectedly however, in our study the underlying microangiopathy with increased microcapillary leakage didn't aggravate post-operative changes. Also, Inflammation may be upregulated also by cataract removal or phacovitrectomy. Intriguingly it seems, as noticed by Sayed M., *et al.* the higher postoperative inflammation and IOP following vitrectomy that tend to occur more in diabetic than in non-diabetic eyes, especially when combined with endolaser photocoagulation, increases the likelihood of wound-sealing until the point that natural wound healing takes place, and reduces the susceptibility to wound sealing-related complications following sutureless vitrectomy [11], as inflammation leads to uveal congestion which in turn approximates the position of the internal orifice. Moreover, removing the ILM eliminates the scaffold for proliferating astrocytes on the retinal surface, alleviating further leakages or retinal re-detachment.

The strength of this study is the intervention of numerous highly qualified and experienced four retina surgeons. In another study [16] we carried out an analysis per surgeon, no statistical difference was shown between them (P = 0.392 with Kruskal-Wallis Test and P = 0.749 with Steel-Dwass- Critchlow-Fligner/bilateral test for PPV surgeries). This reduces the bias failure rate outcome intra-operatively - across a single large population study within 6 months to 3 years follow up for recidivism. Our study excluded patients with follow-up inferior of 6 months. Mansouri., *et al.* [15] required a minimum follow-up of 1 month and found that the average time to redetachment was between 35 to 45 days. Additionally, Kinori., *et al.* [13] defined primary failure as redetachment observed within 8 weeks from the surgical procedure. Thus, our minimum follow-up is yet stricter and reduces the bias of RD reoccurrence due to unpredictable operative subventions.

However, while diabetes is a major risk factor for tractional RD and cataract the risk factor for rhegmatogenous RD [14] and recidivism, we did not take those factors into consideration in our study. Also, we did not study separately the effects of tractional, rhegmatogenous and exudative RD on recidivism because global recidivism rates were expected to be low. One other limitation factor may be the low number of diabetic patients compared to non-diabetic patients (38 vs 755 respectively).

Conclusion

Favorable anatomic retinal reattachments in selected patients with traction/rhegmatogenous RD can indeed be achieved similarly for diabetic and non-diabetic eyes, following initial management with PPV.

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Volume 9 Issue 7 July 2018