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REVIEW ARTICLE

Surgical Management of Proliferative Diabetic Retinopathy

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ABSTRACT

Diabetes is fast becoming a global pandemic. Complications of diabetic retinopathy are the leading cause of blindness in the working age group. While medical interventions and lasers are effective at reducing the frequency of severe vision loss from Proliferative diabetic retinopathy, in a large percentage of individuals surgical intervention may be required to address complications. This review discusses the present indications, techniques and challenges vis-à-vis surgical management of PDR.

Keywords: Diabetic retinopathy, Proliferative Diabetic Retinopathy, Vitrectomy, Vitreous Hemorrhage, Tractional Retinal Detachment

Introduction

Diabetes Mellitus (DM) is fast emerging globally as a public health challenge. The estimated worldwide prevalence of diabetes is 2.8%, which is projected to reach 4.4% by 2030 [1]. All Diabetics are at risk of developing Diabetic Retinopathy, which is one of the leading causes of blindness in the working population. The prevalence of diabetic retinopathy increases with duration of diabetes [2].

As Diabetes damages the retinal blood vessels they either start to leak or get occluded. In the early stages these lead to changes classified broadly as Non-proliferative Diabetic Retinopathy (NPDR). However, with time progressive retinal ischemia results in the development and proliferation of new blood vessels leading to the stage of Proliferative Diabetic Retinopathy (PDR).

Proliferative vessels usually arise from retinal veins and often begin as a collection of multiple fine vessels. With time these new blood vessels tend to grow along the path of least resistance and also more easily on a preformed connective tissue framework, like a shallowly detached vitreous face. As the new vessels proliferate they also undergo fibrotic changes leading to the formation of contractile membranes [3]. These membranes pull on the blood vessels and the retina, resulting in vitreous hemorrhage (VH) or pre-retinal hemorrhage (PRH), tractional retinal detachment (TRD), or combined retinal detachment (CRD) [4].

There are different options to tackle PDR depending on the severity of the disease. The Diabetes Control and Complications Trial (DCCT) [5] and the United Kingdom Prospective Study (UKPDS) [6] established that control of blood glucose and blood pressure can prevent progression to PDR or further deterioration in patients already suffering from the same. The Diabetic Retinopathy Study (DRS), conducted in the 1970s by the National Eye Institute showed that, Panretinal Photocoagulation (PRP) reduces the risk of severe visual loss by more than 50% in eyes with PDR [7]. The recently published DRCR.net Protocol S trial showed that among eyes with PDR, treatment with Ranibizumab alone resulted in visual acuity that was non-inferior to PRP treatment at two years [8] and in eyes with central DME at baseline Ranibizumab gave superior improvement in visual acuity compared to PRP.

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Despite these options, patients with PDR often require surgical treatment. Patients often present late in the advanced stage of disease with retinal detachment that is not amenable to medical management. In addition, despite medical management including laser photocoagulation and tight systemic control, nearly 5% of patients show continued progression of retinopathy and require surgical intervention [9]. This review discusses the present indications, techniques and challenges vis-à-vis surgical management of PDR.

Indications for Surgery

Vitreous hemorrhage

Dense, non-resolving Vitreous hemorrhage (VH) was the earliest indication for vitrectomy in PDR in the 1970s [10]. The Diabetic Retinopathy Vitrectomy Study (DRVS) showed a clear benefit from earlier surgery, defined as surgery within 1-4 months from onset [11]. The benefit is greater in Type 1 diabetics and may be due to the greater incidence of Diabetic Maculopathy and pre-existing posterior vitreous detachment in the elderly Type 2 DM patients. With improved surgical techniques the results of PPV for non-resolving vitreous hemorrhage has improved compared to the results seen in DRVS while, the threshold to operate has decreased [12]. Today most surgeons do not wait beyond 1 month [13]. If surgery is deferred, ultrasonography should be performed at regular intervals to make sure that TRD is not developing behind the VH (Figures 1 and 2).

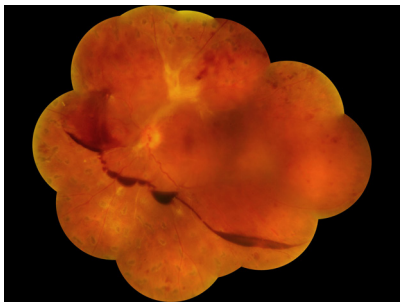

Figure 1: *Pre-operative fundus photo of the left eye of a 54 year old female, with proliferative diabetic retinopathy, dense vitreous hemorrhage and fibro-vascular proliferation along the supero-temporal arcades Visual acuity hand movements only.*

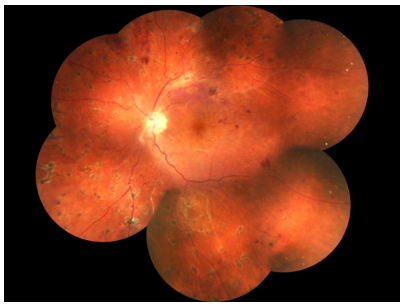

Figure 2: *Post-operative fundus photo of the same eye, 3 months after vitrectomy with membrane peeling, endolaser and gas tamponade (Visual acuity 20/40).*

Tractional retinal detachment

With time new blood vessels grow along the posterior hyaloid using it as a scaffold and undergo fibrotic changes. As the vitreous shrinks slowly in a Diabetic eye it drags on the fibro-vascular membranes and the underlying retina due to vitreo-retinal adhesions resulting in the development of a TRD [14]. Most TRDs generally begin over the arcades and progresses slowly towards the macula. TRD which is in the periphery, away from the macular area and not associated with any significant VH has been traditionally observed [15]. However, with recent improvements in functional and anatomic outcome post vitrectomy, an earlier surgical approach seems reasonable [16]. Once the TRD starts involving the macula or threatens to involve the same, one need to plan surgery. Surgical outcomes are better in patients with recently reduced vision and poorer in patients with longstanding macular traction [17] (Figures 3 and 4).

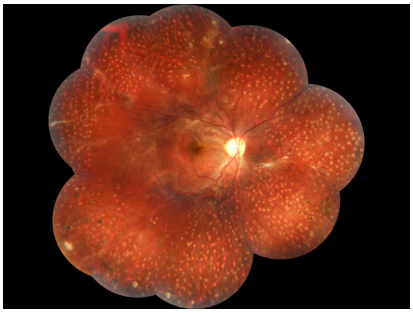

Figure 3: *Pre-operative fundus photo of the right eye of a 44 year old male, with proliferative diabetic retinopathy, scars secondary to post Pan-retinal photocoagulation and fibro-vascular proliferation at the disc extending along the supero-temporal arcades and leading to tractional detachment of the macula (Visual acuity hand movements only).*

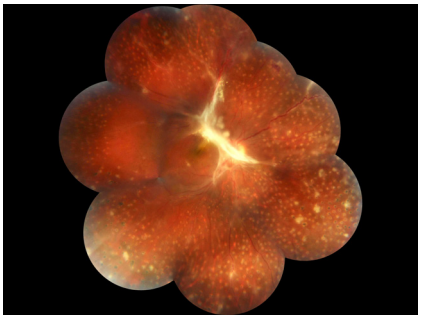

Figure 4: *Post-operative fundus photo of the same eye, 5 months after initial vitrectomy with membrane peeling, endolaser, silicone oil tamponade and subsequent silicone oil removal (Visual acutity 20/125).*

Combined tractional and rhegmatogenous retinal detachment

As the fibro-vascular proliferations develop this results in progressive traction and membrane contraction which may lead to the development of retinal breaks. The development of retinal breaks converts a TRD into a combined mechanism RD (CRD). These breaks are often

small, located posteriorly, paravascular or immediately adjacent to vitreo-retinal tractions and retinal elevations [18]. The outcome of surgery will depend upon the location and extent of the retinal detachment. Eyes having good pre-operative visual acuity have good prognosis whereas, eyes with macular heterotopia have worse outcomes [19]. Vitrectomy with Silicone oil tamponade is frequently indicated in particularly severe cases. Though these cases show a high rate of reattachments however, the chance of visual recovery is just moderate. Still vitrectomy with silicone oil is recommended as it can prevent further complications such as Neovascular Glaucoma and Phthisis (Figures 5 and 6).

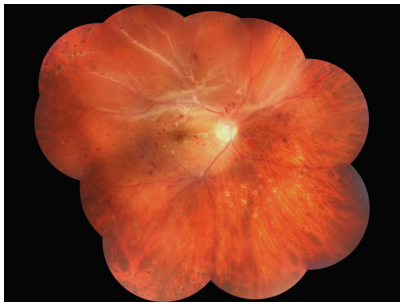

Figure 5: *Pre-operative fundus photo of the right eye of a 57 year old female, with proliferative diabetic retinopathy, few scattered scars secondary to post Pan-retinal photocoagulation and fibro-vascular proliferation with superior combined mechanism detachment of the retina, threatening the fovea (Visual acuity <20/400 only).*

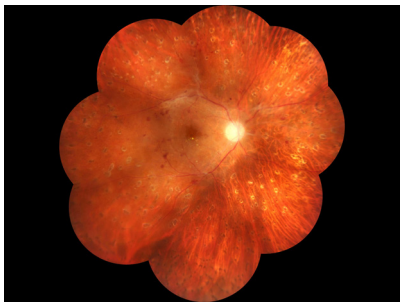

Figure 6: *Post-operative fundus photo of the same eye, 2 months after initial vitrectomy with membrane peeling, endolaser and gas tamponade (Visual acuity 20/19).*

Pre-macular hemorrhage

In these cases the blood is trapped between the posterior hyaloid interface and the internal limiting membrane. The hemorrhage usually results in significant visual loss. It may be associated with fibro-vascular proliferations, pre-retinal membrane formation, or tractional macular detachment, which are all indications for early vitrectomy [20]. Less invasive methods of managing pre-macular blood includes observation, laser membranotomy, or intravitreal injections with recombinant tissue plasminogen activator or gas.

Techniques of PPV in Diabetic Retinopathy

All patients need to be seen by a physician or endocrinologist to ensure stable systemic parameters before any procedure is undertaken. Systemic parameters influence the timing as well as prognosis of the surgery [21]. Every patient must undergo a thorough ophthalmic evaluation and one must try to correlate the history of visual decrease with existing anatomic changes. This correlation is a major prognostic factor for surgical success [22]. If possible one may advise fluorescein angiography and/or optical coherence tomography to assess the extent of neo-vascularizations, retinal iscaemia, vitreo-retinal tractions, macular edema and epi-retinal membranes [23]. In patients of Type 1 DM with severe PDR, there is strong evidence of the value of performing as much PRP as possible prior to surgery, especially in the anterior periphery to minimize the risk of further anterior neo-vascularizations or fibro-vascular proliferations [24].

Role of Preoperative Intravitreal Bevacizumab

Intra-operative bleeding from the fibro-vascular membranes is the major intraoperative complication in vitrectomy for PDR. Pretreatment with intravitreal Bevacizumab, 3-4 days prior to surgery helps in reducing intra-operative bleeding, thus facilitating fibro-vascular membrane peeling [25]. There is however, one important issue to remember when using Pre-operative Bevacizumab. 3.5% of PDR cases treated pre-operatively with Bevacizumab showed development or progression of TRD [26]. To reduce the risk of TRD, intravitreal bevacizumab should ideally be given within 4 days of surgery and one should avoid a higher dose (2.5 mg) [27].

Anaesthesia

The surgery can be done under general or local anesthesia. The chosen form depends on the patient's mental or physical condition, expected complexity and duration of the case or simply surgeon's choice. Close monitoring of vitals is of utmost importance, even if the surgery is done under local anesthesia.

Surgical techniques

Due to improved instrumentation, currently, smaller gauge trans-conjuctival PPV is being favored compared to 20 gauge PPV with faster recovery in patients with PDR [28] and reduced incidence of peripheral sclerotomy-related retinal breaks [29]. Micro-incisional vitrectomy also minimizes inflammation and post-operative discomfort to the patient. However, their efficiency in complex advanced diabetic retinopathy is still being debated. In recent literature, 23- and 25-gauge systems show more stable and reproducible results even in severe PDR compared with 27-gauge [30, 31].

The first step of the surgery is to remove the central or 'core' vitreous and identification of the posterior hyaloid face (PHF). If there is significant retro-hyloidal bleed, an opening is created in the PHF and retro-hyaloidal blood

is aspirated to gain a good view of the underlying retina [32]. In case the PHF cannot be identified with certainty 2-4 mg of traimcinolone acetonide may be injected to stain the same. Once the PHF has been identified and the precise visualization of the retina is achieved, the surgeon has to decide if there is pre-existing complete Posterior Hyaloid separation or Not.

In patients where complete Posterior Hyaloid separation exists, as the PHF is carefully removed areas of neo-vascular membranes and multiple small sources of bleeding can be identified. Diathermy is used to cauterize the bleeding sources, and the vitreous is removed further out to the periphery. During peripheral dissection any blood located anteriorly is thoroughly removed to prevent post-operative bleeding, tissue contraction, and rubeosis iridis. A full scatter PRP is done and the macula examined for any residual pre-retinal or epiretinal membranes. If present these membranes are removed with or without the internal limiting membrane.

In patients where complete Posterior Hyaloid separation is absent, a thorough core vitrectomy is done to gain a sufficient view of the areas of vitreo-retinal adhesions. If there is wide separation between the vitreous and the retina then, circumferential release of the antero-posterior traction can be done with the vitreous cutter itself. In patients with dense vitreo-retinal adhesions along the areas of vascular membranes, one has to be very careful to avoid injuring the retina. These vascular membranes cannot be simply peeled from the retinal surface as it results in bleeding and retinal tears [33, 34]. The following techniques are useful in dissecting these densely adhered surface membranes.

Segmentation

In this technique the surgeon releases all circumferential traction around the membranes, with the help of a vertical cutting scissors or vitreous cutter and dissects the membranes into small segments. These segments can be left as remnants center on neovascular pegs.

Delamination

In this technique the surgeon removes the the fibrovascular membranes from the surface of retina with the help of a Horizontal scissors or the vitreous cutter. The key step in Delamination is to correctly identify the plane between the membrane and the retina [35]. In cases where there are multiple isolated adhesions with adequate space between retina and vitreous the dissection maybe performed with a vitreous cutter. In cases with densely adherent membranes one may use Bi-manual surgical techniques, with a curved scissors in one hand and a forceps in the other [31]. It is safest to start the dissection around the optic disc and extend centripetally.

Once all membranes have been dissected, the vitreous is removed till periphery and a full scatter PRP done. The last step is to choose a tamponading agent. Various gases and liquids are available for this purpose. The choice depends on the severity of the disease, desired duration of tamponade, likelihood of recurrent hemorrhage, status of the fellow eye, patient's physical status and ability to comply with follow-ups [36, 37].

Complications

Intra-operative complications

There may be intra-operative corneal edema due to abnormal basement membrane leading reduced epithelial adherence in Diabetic patients [38]. Use of visco-elastic and corneal lubrication reduces the need for corneal debridement [39]. In nearly 1/3rd of the patients there may be creation of iatrogenic retinal breaks, more so in eyes where membranes are fibrous while the retina is thin and atrophic [40]. The major complication during surgery for PDR is intra-operative bleeding. Unless controlled properly, this can prevent successful completion of surgery. Sometimes transient intra-ocular pressure (IOP) elevation might be sufficient to control bleeding, but mainly diathermy should be used to cauterize all bleeders.

Post-operative complications

Up to 35% of the diabetic eyes undergoing vitrectomy have been reported to have postoperative intra-ocular pressure (IOP) of $\geq$ 30 mm Hg [41]. One should carefully monitor the IOP post-operatively. Nearly 1/3rd of the eyes operated for PDR develop visually significant cataract post-operatively [42]. As diabetic vitrectomies combined with lens surgery and IOL implantations are increasing in numbers, this problem has become rare. Postoperative vitreous hemorrhage following PPV for PDR has been reported in 12%-63% of cases and may occur within the first few weeks or even months later [43, 44]. The rates of post-operative bleed following 23-gauge (17%) and 20-gauge vitrectomy (26%), is comparable [45]. Inadequate PRP, phakic eye and younger age have been reported to be associated with post-operative recurrent bleed in diabetics [46]. The management of post-operative VH includes observation, vitreous cavity lavage, or repeated vitrectomy. Serial ultrasound is mandatory in patients being observed and with poor retinal visualization. The development of iris neovascularization following diabetic vitrectomy has significantly reduced following the development of endolaser delivery system [47]. Some young patients with long standing diabetes and extensive retinal ischemia may develop anterior hyaloidal fibrovascular proliferation (AHFVP). Patients with AHFVP may present with rubeosis iridis, peripheral TRD, or hypotony [48] or as VH, 3-12 weeks after vitrectomy probably due to increased VEGF levels in the postoperative period [49]. Additional panretinal photocoagulation, cryotherapy of sclerotomy sites, and surgical intervention are usually necessary [50]. The functional prognosis in eyes with AHFVP is always poor; therefore, all efforts for prevention and early detection of AHFVP should be made [48].

Conclusion

The role of pars plana vitrectomy is unquestionable for managing complications of proliferative diabetic retinopathy including those that were previously considered blinding. The main surgical principles are removal of vitreous blood, relief of vitreo-retinal tractions, laser treatment of all ischemic retinal areas and application of tamponades with or without anti-angiogenic agents. With newer improved techniques and pharmacologic interventions like minimally invasive vitreoretinal surgery and intravitreal bevacizumab, early vitrectomy is favored due to better visual outcomes.

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