Surgical management of diabetic retinopathy

Tratamento cirúrgico da retinopatia diabética

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ABSTRACT

Diabetic retinopathy is the leading cause of blindness among the working population in the developed world. The prevalence of diabetic retinopathy increases with duration of diabetes, and nearly 100 percent of patients with type I diabetes and more than 60 percent of those with type II have some signs of diabetic retinopathy after 20 years. A number of approaches have proved to be useful in the treatment of diabetic retinopathy, such as laser photocoagulation and tight systemic control of blood glucose, lipids, cholesterol and blood pressure. Unfortunately, in many patients the retinopathy progresses in spite of the best efforts on the part of the patient and of the ophthalmologist. Many such eyes may be helped by vitrectomy surgery, however. About 5 percent of patients with proliferative diabetic retinopathy, as well as carefully selected patients with diabetic maculopathy, require pars plana vitrectomy, despite ostensibly adequate laser treatment and good glycemic and hypertensive control. This article reviews the current indications for vitreous surgery in severe diabetic retinopathy and strategies and techniques employed to minimize surgical complications.

Keywords: *Diabetic retinopathy/surgery; Retinal diseases/surgery*

RESUMO

A retinopatia diabética é a causa mais frequente de cegueira na população ativa nos países desenvolvidos. A prevalência da retinopatia diabética aumenta com a duração da diabetes, e praticamente 100% dos pacientes com diabetes tipo I (DM I) e mais do que 60% dos pacientes com o tipo II (DM II) apresentarão algum sinal de retinopatia após 20 anos. Além de um controle sistêmico rigoroso dos níveis glicêmicos, lipídicos, colesterol e da pressão arterial, o exame oftalmológico de rotina, com a identificação precoce da retinopatia diabética, podem detectar anormalidades em estágios primários, o que possibilita o tratamento ainda na fase inicial do problema; o uso adequado da fotocoagulação e a utilização da terapia antiangiogênica pode reduzir o número de pacientes com hemorragia vítrea ou descolamento tracional da retina. Infelizmente, em vários pacientes, a retinopatia progride mesmo com as melhores condutas tomadas pelo paciente e pelo oftalmologista, embora vários olhos podem se beneficiar com o tratamento cirúrgico, a vitrectomia posterior via pars plana. Esta revisão apresenta as indicações atuais para cirurgia vitreorretiniana em pacientes portadores de retinopatia diabética proliferativa.

Descritores: Retinopatia diabética/cirurgia; Doenças retinianas/cirurgia

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Introduction

Diabetic retinopathy (DR) is the most frequent cause of blindness among the economically active population in developed countries. The prevalence of DR increases with the duration of diabetes[1], and almost 100% of patients with type 1 diabetes (DM 1) and more than 60% of patients with type 2 (DM 2) will present some sign of DR after 20 years. A number of established guidelines are useful in the treatment of DR, such as laser photocoagulation and anti-VEGF therapy, as well as strict systemic control of blood glucose levels, lipids, cholesterol and blood pressure[2,3]. Unfortunately, in many patients, retinopathy progresses despite the adoption of best practices by the patient and the ophthalmologist. Many eyes can benefit from surgical treatment, i.e. pars plana vitrectomy[4]. About 5% of patients with proliferative DR, as well as some patients with diabetic maculopathy, require vitrectomy despite adequate laser treatment (photocoagulation) and good control of blood glucose and blood pressure[5]. This review illustrates the current indications for vitreoretinal surgery in advanced DR and strategies and techniques used to minimise surgical complications.

Pathogenesis of diabetic retinopathy

Diabetic retinopathy is a microvascular complication of diabetes characterised by functional loss of pericytes and progressive capillary occlusion, causing retinal ischemia and breakdown of the blood-retinal barrier.This can result in oedematous changes in non-proliferative diabetic retinopathy (NPDR) and neovascular proliferation and the formation of contractile fibrocellular membranes on the retinal surface in proliferative diabetic retinopathy (PDR)[6,7].

Visual loss in RDP is caused by a combination of retinal ischemia, vitreous haemorrhage and/or tractional retinal detachment (TRD). It usually starts with neovascularisation of the optic disc (NVD) and retina (NVE).The growth of neovessels (NVs) occurs simultaneously with fibroblast proliferation in the vitreoretinal interface, using the posterior hyaloid as a support[8]. Subsequent contractions of fibrocellular membranes cause progressive traction on NVs, resulting in intravitreous and/or subhyaloid haemorrhage. Pronounced and generalised traction can be complicated by TRD or a combination of tractional and rhegmatogenous detachment, known as combined retinal detachment (RTRD)[9].

Indications for surgery in PDR

Pars plana vitrectomy (PPV) to treat complications of PDR was first described over 25 years ago[10]. PPV allows the removal of media opacity such as vitreous haemorrhage, as well as releasing any vitreoretinal traction. Furthermore, intraoperative photocoagulation of the retina helps to stabilise intraocular vasoproliferation[9,11]. Ocular ultrasonography in patients with dense opacities is essential to the diagnosis of retinal detachment and to differentiate TRD and RTRD (combined DR) preoperatively. Even though the final visual acuity after vitrectomy can vary greatly, most patients benefit from the procedure[12,13].

Vitreous haemorrhage

Vitreous hemorrhage is the most frequent complication of DRP and can cause a significant reduction in visual acuity, interfering with clinical examination and treatment. In patients with DM 2, recent vitreous hemorrhage can be treated conservatively in the hope of spontaneous resolution, so that laser treatment can be administered. Chronic and persistent vitreous haemorrhage (older than 3 months) can be an indication of PPV and endolaser photocoagulation. On the other hand, the *Diabetic Retinopathy Vitrectomy Study* (DRVS) showed that early surgery in patients with DM I is clearly beneficial, as these patients tend to develop more aggressive fibrovascular proliferation[14,15]. The study also showed that 25% of patients undergoing early vitrectomy have a good recovery of visual acuity, around 20/40 or better, compared with 15% of patients treated conventionally[15]. Although the procedure entails a higher risk, it is important to note that the surgical technique (e.g. use of the endolaser) has evolved considerably since the completion of the study.

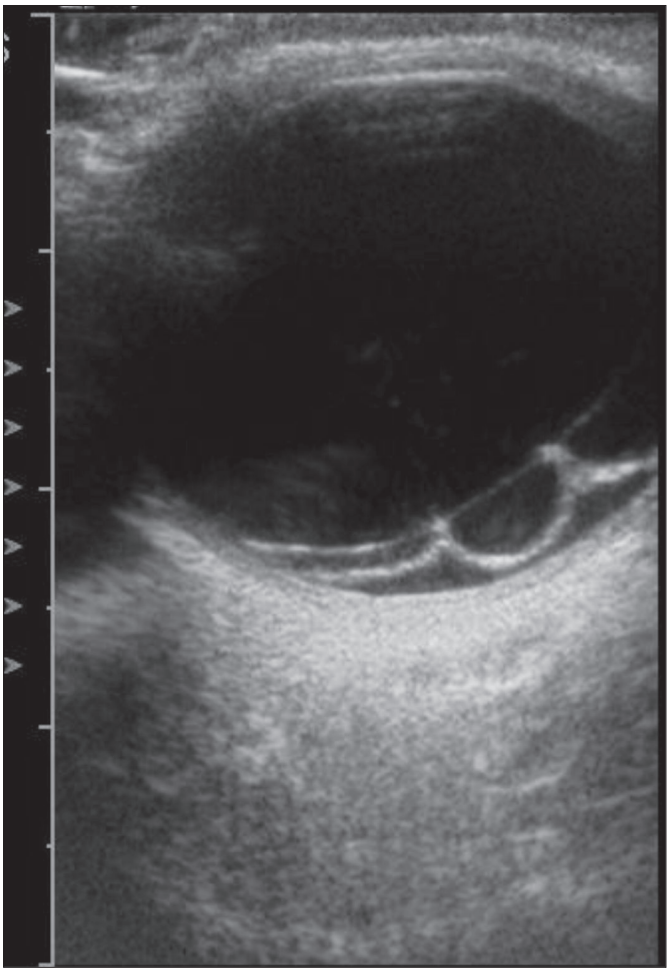

Figure 1. Ultrasonography: tractional retinal detachment (TRD)

Early vitrectomy can also be considered in cases of vitreous retrohyaloid haemorrhage, as the blood in this space tends to be reabsorbed more slowly than when it crosses the posterior hyaloid into the vitreous cavity. The correct timing for surgery is also influenced by the condition of the contralateral eye and the presence of other conditions such as TRD with macular involvement and/or neovascular glaucoma (Figure 1). In the latter, waiting for the haemorrhage to reabsorb can cause irreversible damage.

Other indications for early surgery include no previous photocoagulation and patients who require rapid visual recovery (e.g. professions requiring good stereopsis)[16].

Retinal detachment

Tractional retinal detachment (TRD) involving the fovea causes significant visual loss and is a common indication for surgery in patients with DRP (Figure 2). In a recent study, 57% of eyes suffering from TRD with macular involvement achieved a visual acuity of 20/400 or better, while 84% of eyes without macular detachment achieved a visual acuity of 20/400 or better[13].

The urgency for vitreoretinal surgery varies from patient to patient, but in most patients surgical planning is better when all the necessary elements, such as the operating room, medical staff and supplies, are available.

Eyes recently affected by foveal detachment are more likely to progress with visual recovery than eyes with an older history for the condition, even if a good anatomical result is achieved[17].

Extramacular TRD can be managed conservatively, since it remains stable and the risk of intraoperative or postoperative complications may be too high[18]. Another study showed that only 14% of eyes with extramacular TRD had vision loss in one year[19]. Still, PPV may be occasionally considered even before macular involvement when photocoagulation is not possible due to vitreous hemorrhage or fibrovascular tissue on the retinal surface, and also when progression of paramacular tractional detachment is observed.

Combined retinal detachment (RTRD) is relatively uncommon and can occur both during the fibrovascular proliferation stage or as a late complication. In most cases, retinal tears are located in the region posterior to the equator and are often associated with highly adherent fibrovascular membranes.This type of detachment progresses rapidly, resulting in a bullous configuration of the subretinal fluid and extending out to the ora serrata. Immediate PPV is usually necessary in order to release the vitreoretinal tractions to allow photocoagulation around the tears after intraocular tamponade with air, gas or silicone oil[20]

Surgical indications in non-proliferative diabetic retinopathy (NPDR)

Macular oedema

Diabetic macular oedema (DMO) or retinal thickening is the leading cause of reduced visual acuity in patients with diabetes mellitus. While the pathogenesis of DMO is multifactorial, the vitreous may contribute to the development of DMO in some cases[21]. Vascular leakage and ischemia are responsible for much of the visual loss related to diabetic maculopathy. The vascular endothelial growth factor (VEGF), considered as the most important growth factor, causes a breakdown of the inner blood-retinal barrier, resulting in an increase of retinal vascular permeability and retinal oedema[22]. While the healthy retina also contains VEGF, changes induced by diabetes cause affect its regulation[23]. Thus, VEGF levels are very high in eyes with DMO[24].

The role of the vitreous in the development of DMO is not yet fully understood, but it is intriguing that studies evaluating its natural history show that the macular oedema seems to resolve followed by spontaneous vitreomacular separation.While PPV has shown good anatomic and functional results in eyes with a stretched or thickened posterior hyaloid membrane and macular traction (Figure 3)[21,25], other studies suggest that PPV can also be beneficial in cases with no clinical evidence of traction. It is believed that after removal of the vitreous cortex, with or without internal limiting membrane (ILM) peeling, the release of

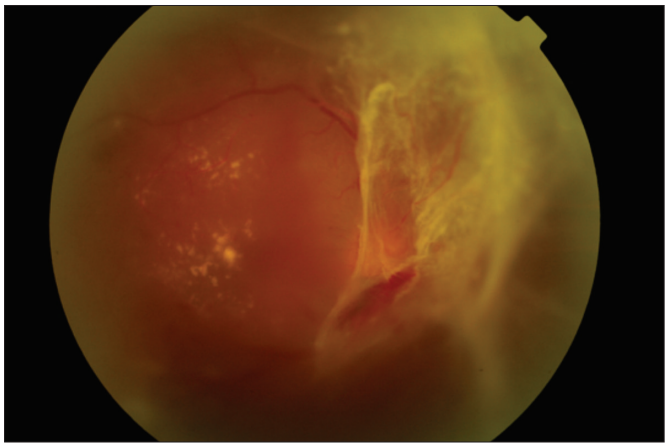

Figure 2. Right eye of a patient with tractional retinal detachment with macular involvement

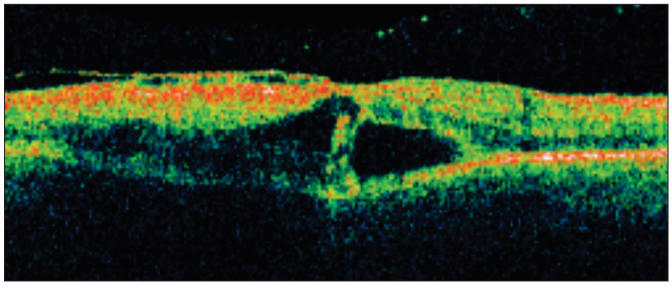

Figure 3. Optical coherence tomography (OCT): stretched/thickened posterior hyaloid in a patient with diabetic retinopathy

subclinical vitreomacular tractions improves retinal oxygenation and/or reduces the concentration of growth factors (e.g. VEGF) in the posterior segment, as well as other cytokines released by the ischemic retina[26,27].

In a randomised controlled trial comparing PPV with ILM removal versus focal laser photocoagulation, there was no difference between the two treatments in anatomical or functional outcomes[28]. A randomised pilot study on patients with DMO without macular traction also showed no benefit in terms of visual acuity or macular thickness[29].

Surgical techniques

When there is vitreous hemorrhage, standard PPV is performed first and the posterior hyaloid is identified; if there is a large amount of blood behind the posterior hyaloid, a small opening is created on it to aspirate the retrohyaloid blood, providing an adequate view of the retina[30]. It is essential to release any traction by pre-existing membranes in the retina. Such membranes are usually vascularised, so they can not simply be removed from the retinal surface as this may result in significant haemorrhage and/or retinal tears[30,31]. The main surgical techniques to manipulate epiretinal fibrotic tissue are: segmentation, delamination, en bloc resection, and bimanual dissection; these are employed in vitrectomy surgery in diabetic patients [30,31,32].

Segmentation

Segmentation is based on the dissection of epiretinal fibrosis, usually with vertical scissors or with the tip of the vitreophage. The procedure starts with a 360-degree removal of the posterior hyaloid followed by identification of the cleavage plane between the retina and the fibrotic membranes. The tangential traction is

reduced with the help of scissors, cutting the membranes and separating them from the epicenters. This technique is used to release circumferential tractions when other methods, such as delamination, are difficult due to the torn retina's mobility. It is not necessary to completely remove the membranes; at the end of the procedure, small fibrotic islands usually remain on the retina. This can be considered as a disadvantage of this technique, since those residual areas of fibrovascular tissue may proliferate and bleed again[30,31,32].

Delamination

The risk of new postoperative haemorrhage can be reduced with the complete removal of fibrovascular membranes adhered to the retina. In this technique, tissue removal is made through horizontal dissection in the cleavage plane between the retina and the fibrosis. Finding the correct cleavage plane between the posterior hyaloid and the retina near the vascular epicenter is crucial to avoid iatrogenic rupture[30,31]. Horizontal scissors are generally used, and the fibrotic membrane is usually completely removed. As in the previous technique, is posterior hyaloid is removed at the start of the procedure. After removal, the membrane is removed with the vitreophage[30,32,33].

En bloc resection

En bloc resection uses the techniques of membrane delamination, but without removing the hyaloid. The posterior hyaloid is delicately separated, remaining adhered to the fibrotic tissue and the vitreous base. The difference in this technique is that the hyaloid remains intact. A small opening is made in the partially-detached posterior hyaloid through which horizontal scissors can be inserted in the retrohyaloid space. This technique uses anteroposterior hyaloid traction to help remove the membranes. All the hyaloid and the fibrous tissue are removed as a single piece, using forceps and scissors, and the separated tissues are then cut and aspirated through the vitrectomy probe[32,33].

Bimanual dissection

In combined detachments it can be useful to combine delamination and segmentation, as it is difficult to completely separate fibrotic membranes from a detached retina. The bimanual dissection technique can be employed in complex cases using an auxiliary light source, allowing the surgeon to use two instruments for dissection[30,32].

With the evolution of vitrectomy systems and devices, especially more distal openings in vitrectomy probes, most membrane and TRD procedures can be performed with the vitreophage probe only. The vitrectomy probe is positioned close to the membranes, which are removed by cutting and aspiration; the procedure should be performed with care in order to avoid iatrogenic ruptures.

In order to achieve the best results for the patient, a combination of the previously described techniques can be used.

Laser (Photocoagulation)

Endolaser photocoagulation is always used, even in eyes previously treated with panphotocoagulation, with the goal of reducing the neovascular stimulus and minimising or delaying recurring hemorrhage. A review of the entire peripheral retina is performed before the end of surgery in order to identify any pre-existing retinal tear or iatrogenic tears (e.g. sclerotomy tears). Should a tear be found, it should be treated with photocoagulation or cryotherapy associated with a tamponading agent (e.g. air, expanding gas or silicone oil). In a prospective study of 174 consecutive vitrectomies, 39% of operated eyes had retinal tears, of which 27% were posterior and occurred during membrane dissection, while 17% of eyes had tears at the sclerotomy site. Overall, 49% of eyes required some tamponading agent: 8% air, 24% SF6, 10% C3F8, and 7% silicone oil[13].

Vitrectomy in diabetic macular oedema (DMO)

PPV for DMO can be performed with or without removing the internal limiting membrane. Chromovitrectomy with dyes such as indocyanine green and brilliant blue can be used during vitrectomy in order to dye the internal limiting membrane for improved visualisation.

A comparative study of vitrectomy for the treatment of clinically-significant diffuse macular oedema showed a structural improvement in optical coherence tomography (OCT), with foveal thickening and significant improvement in macular volume, although visual acuity improvement was limited 12 months after surgery[34].

Antiangiogenic therapy

Antiangiogenic agents were introduced in ophthalmic practice a few years ago for the treatment of age-related macular degeneration. Several studies have also demonstrated their benefits in proliferative diabetic retinopathy[35,36]. These studies describe the use of ranibizumab and bevacizumab as monotherapy in patients with vitreous hemorrhage or as preparation for vitrectomy. Temporary interruption of neovascular activity seems to promote the absorption of the vitreous hemorrhage. In more complicated cases with fibrovascular proliferation and TRD, these drugs seem to play an important role in the rapid regression of retinal and iris neovascularisation and facilitate the removal of membranes, directly reducing intraoperative bleeding[37-39]. Some cases show a worsening of TRD or even the onset of associated rhegmatogenous DR after administration of antiangiogenic agents. These complications usually occur due to vitreous contraction in the first 2-3 weeks; it is therefore important to perform vitrectomy up to two weeks after injection of the antiangiogenic agent[38,40].

Surgical complications

The main surgical complications in diabetic patients undergoing PPV include recurrent vitreous haemorrhage, rhegmatogenous retinal detachment (RRD), rubeosis iridis and neovascular glaucoma.

Vitreous hemorrhage in the immediate postoperative period is common and usually resolves spontaneously after a few weeks. Vitreous hemorrhage in the late postoperative period occurs in only 10% of diabetic eyes and may be related to neovascular proliferation in the vitreous base, usually at the site of sclerotomy. In a recent study, the most common postoperative complication was vitreous haemorrhage, which occurred in 22% of eyes[13]. Previous cryotherapy, confluent endolaser photocoagulation posterior to the ora serrata, and transscleral laser can reduce the risk of recurrent fibrovascular proliferation and haemorrhage[41]. Periodic ultrasound imaging in eyes whose fundus cannot be visualised should be used to exclude retinal detachment. Rhegmatogenous retinal detachment (RRD) after vitrectomy is usually due to retinal tears not found intraoperatively and requires urgent treatment to prevent the development of proliferative vitreoretinopathy (PVR) and/or rubeosis iridis[14,42]. In another study, the incidence of DRR was 4.7%[43]. The risk of RRD after vitrectomy in diabetic patients seems to be decreasing, probably due to the use of systems for

wide-angle viewing, which provides a more detailed and accurate view of the peripheral retina[43,44], and new 23-gauge and 25-gauge vitrectomy systems[45,46]. Retinal detachment is associated with rubeosis iridis in up to 83% of cases[32].

The incidence rate of neovascular glaucoma varies according to the preoperatory severity of the case, affecting up to 20% of operated patients[32].

In the anterior segment, corneal epithelial defects are now also less common due to the introduction of the noncontact visualisation systems (e.g. BIOM). Although nuclear cataract usually develops after PPV, this is less common in diabetic patients. A study showed an incidence of 15% for cataract removal after PPV in diabetic patients, compared to 66% and 53% after vitrectomy for the treatment of macular hole and epiretinal membrane, respectively[47]. Combined PPV and phacoemulsification with implantation of intraocular lens ("phacovitrectomy ") is becoming more popular. However, it is not recommended for patients with severe retinal ischemia, rubeosis iridis and patients with TDR[48].

Final considerations

According to the World Health Organisation (WHO), approximately 150 million people are currently affected by diabetes, a number that could double in the next 10-15 years. Diabetic retinopathy is the leading cause of blindness among the economically-active population in industrialised countries, corresponding to 30% of blind patients. Early diagnosis and timely treatment can reduce the risk of blindness among these patients by more than 80%.

In recent years, numerous advances have been published in the treatment of diabetic retinopathy, thanks to multicenter studies and new prospects for better results with the advent of better surgical techniques, modern equipment and new intravitreal medications.

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