·综　　述·

抗血管内皮生长因子在辅助增生性糖尿病视网膜病变手术治疗中的应用

李冰　综述　叶俊杰　审校
100730 中国医学科学院　北京协和医学院　北京协和医院眼科
通信作者：叶俊杰，Email：yejunjie@hotmail.com
DOI：10.3760/cma.j.issn.2095-0160.2017.11.019

【摘要】 增生性糖尿病视网膜病变（PDR）是糖尿病患者严重眼部并发症之一，是导致患者失明的主要原因。玻璃体切除术（PPV）是治疗严重玻璃体积血、增生性糖尿病视网膜病变的有效方法。但是由于 PDR 患者眼内血管内皮生长因子（VEGF）浓度异常增高，使得玻璃体腔内和视网膜表面存在大量的新生血管，极易渗漏、出血，术中常常出现活动性出血而降低手术野的清晰度，降低操作精准度进而影响手术进程。在较严重活动性出血的情况下，继续进行气/液交换可导致血小板的残留，术后再次出现机化膜的概率非常高，严重影响手术的成功率。另外，新生血管可引起术后前房出血、再次玻璃体积血以及视网膜表面出血等，炎症、积血造成的术后高眼压，机化膜再次牵拉视网膜脱离等并发症也将随之而来，严重影响其术后视功能的恢复和远期预后。随着近几年抗 VEGF 药物的广泛临床应用，研究发现 PPV 前玻璃体腔注射抗 VEGF 药物可抑制新生血管的活动性，显著减少术中及术后出血的发生，降低手术难度，缩短手术时间，有效提高手术成功率。本文就抗 VEGF 辅助 PPV 治疗增生性视网膜病变的分子机制、临床应用、有效性及安全性等进行综述。

【关键词】 增生性糖尿病视网膜病变/治疗；血管内皮生长因子；玻璃体切除术

Application of anti-vascular endothelium growth factor in assisted surgery for proliferative diabetic retinopathy

Li Bing, Ye Junjie
Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100730, China
Corresponding author: Ye Junjie, Email: yejunjie@hotmail.com

[**Abstract**] Proliferative diabetic retinopathy (PDR) is one of the serious ocular complications of patients with diabetes mellitus and also the leading cause of blindness. Pars plana vitrectomy (PPV) is an effective treatment for severe vitreous hemorrhage and PDR. The intraocular concentration of vascular endothelial growth factor (VEGF) of patients with PDR usually increase abnormally, which promote growth of neovessels and make it early to leak and bleed. Numerous neovessels in vitreous cavity and retinal surface can lead to intraoperative bleeding and may affect the definition and precision of operation and prolong surgical time. If we conduct gas/fluid exchange regardless of severe active bleeding, proliferate membrane may reoccur at a high rate postoperatively due to the residual platelet and impair the success rate of surgery seriously. In addition, with the high activity of neovessels, anterior chamber, vitreous and retinal hemorrhage may appear as well as other postoperative complications like postoperative high intraocular pressure caused by inflammation or hemorrhage and traction retinal detachment because of reoccurrence of fibro membrane, which directly affect the postoperative visual function recovery and long-term prognosis. As wide clinical application of anti-VEGF agents in recent years, studies found that preoperative intravitreal injection of anti-VEGF drugs assisted PPV can limit the activity of neovessels and significantly reduce the incidence of intraoperative and postoperative bleeding, facilitate operation, shorten surgical time and improve the success rate of surgery. In this paper, the mechanism, effectiveness, clinical utility and safety of anti-VEGF therapy assisted vitrectomy for the treatment of PDR are reviewed.

[**Key words**] Proliferative diabetic retinopathy/therapy; Vascular endothelial growth factor; Pars plana vitrectomy

截至 2013 年，全球已有 3.82 亿糖尿病患者，患病人数仍呈现高速上升趋势，与此同时糖尿病相关并发症的发病率也将逐年上升[1]。糖尿病视网膜病变（diabetic retinopathy，DR）是糖尿病患者常见眼部并发症，1.5% 的糖尿病患者发展至增生性 DR（proliferative DR，PDR）阶段，部分地区甚至有高达 10% 的糖尿病患者的眼部并发症已严重威胁视力[2-3]。在发达国家，DR 是15～64岁人群最主要的致盲原因，对经济和社会发展造成了沉重负担。

1　血管内皮生长因子与 DR

早在 20 世纪 50 年代即有学者提出 DR 的发生与视网膜缺血缺氧所致新生血管形成有关，直到 1994 年该理论首次得到证实[4-5]。玻璃体腔内血管内皮生长因子（vascular endothelial growth factor，VEGF）浓度的异常升高是导致 PDR 发生、进展的重要因素[6-7]。在 VEGF 的 2 种亚型中，VEGF-2 可刺激内皮细胞增生迁移，形成新生血管，从而引起 PDR 患者眼部微血管渗漏[8]。近期的研究还发现，PDR 患者中与 VEGF 相关的多条分子信号传导通路均有不同程度的紊乱，导致玻璃体腔内血管生成/抑制状态失衡[9-11]。PDR 患者玻璃体腔内胎盘生长因子（placental growth factor，PlGF）表达量明显升高，进而加强 VEGF 信号传导[9]。另外患者玻璃体腔内结缔组织生长因子（connective tissue growth factor，CTGF）表达也明显上调，可加快纤维化进程，与 VEGF 协同作用，在新生血管膜纤维机化和牵拉视网膜脱离过程中起重要推动作用[10]。VEGF 分子可诱导细胞内粘附分子 1（intercellular adhesion molecule-1，ICAM-1）的高表达，导致视网膜循环中白细胞瘀滞、聚集，逐渐破坏血-视网膜屏障，造成血管内皮的损害和死亡，进而形成毛细血管无灌注区；随 DR 进展，玻璃体腔中 VEGF 和 ICAM-1 浓度也不断升高，二者间存在显著相关性[12]。VEGF 还可刺激内皮祖细胞（endothelial progenitor cells，EPCs）自骨髓迁徙至视网膜循环中，分泌干细胞因子（stem cell factor，SCE），加快新生血管形成[13-14]。VEGF 还可干扰组织纤溶酶原激活物（tissue plasminogen activator，t-PA）和纤溶酶原激活物抑制因子（plasminogen activator inhibitor，PAI）之间的平衡，使 t-PA 过度活化，PAI 浓度降低，进一步诱发细胞外基质、血管内皮细胞基底膜的破坏和降解[15-16]。VEGF 升高还可介导眼内转化生长因子 β1（transforming growth factor beta-1，TGFβ-1）、白细胞介素 6（interleukin 6，IL-6）等多种炎性因子的高表达，加快 PDR 进程[17]。硫酸乙酰肝素是血-视网膜屏障中基质层的重要组成部分，Abu 等[11]还发现 PDR 患者玻璃体腔中肝素酶浓度较正常人显著升高，加快硫酸乙酰肝素分解，破坏血视网膜屏障，同时诱导 VEGF 表达升高，促进新生血管形成。研究还发现年轻患者硫酸乙酰肝素的异常更为明显，这也在某种程度上解释了为何年轻患者的 PDR 进展难以通过抗 VEGF 治疗得到有效控制[11,18]。

2　抗 VEGF 类药物

基于 VEGF 在 DR 进展中起重要作用，抗 VEGF 药物治疗 DR 的研究也成为近几年的热点。目前常用的抗 VEGF 药物主要有贝伐单抗、雷珠单抗、康柏西普、阿柏西普等生物制剂，其药效均已在临床试验中得到证实[19-20]。贝伐单抗是较早应用于临床的重组抗人 VEGF 单克隆抗体，其玻璃体腔注射可用于治疗年龄相关性黄斑变性（age-related macular degeneration，AMD）、视网膜静脉阻塞及糖尿病黄斑水肿等[21-24]。贝伐单抗可拮抗 VEGF 家族中全部亚型，因而临床效果明显，但可能导致眼内 VEGF 浓度过低，使其正常生理作用受到抑制，加重缺血，继发其他眼部疾患[25]。雷珠单抗是特异性阻断 VEGF-A 的抗 VEGF 类单克隆抗体，其不包含 Fc 片段，相对分子质量更小，也减少了因 Fc 片段所引发的炎症和过敏反应[25]。在新生血管相关眼病的治疗中，雷珠单抗与贝伐单抗相比，视力预后无明显差别，但雷珠单抗玻璃体腔注药所引起的全身并发症的发病率较贝伐单抗减少 17%[26]。阿柏西普则为融合蛋白类抗 VEGF 药物，与 VEGF 的结合力更强。与雷珠单抗不同，阿柏西普除可拮抗 VEGF-A 外，还可抑制 VEGF-B 和胎盘生长因子（placental growth factor，PCGF）的表达[27-28]。研究发现，在 AMD 治疗中阿柏西普每 2 个月注射 1 次即可获得与雷珠单抗每月注射 1 次相似的治疗效果[29]。研究发现，部分湿性 AMD 患者对雷珠单抗和贝伐单抗治疗不敏感，换用阿柏西普后患者黄斑部积液明显减少，视力显著提高[30]。中国自主研发的康柏西普（Conbercept）眼内注射液也是融合蛋白类的抗 VEGF 药物，与 VEGF-A 的亲和力是雷珠单抗和贝伐单抗的数倍，康柏西普对 10 pmol/L VEGF-A_{165} 的 50% 抑制浓度（50% inhibitory concentration，IC50）仅为7～10 pmol/L，而雷珠单抗和贝伐单抗则分别为 343 pmol/L 和 423 pmol/L[31]。康柏西普于 2013 年在中国批准上市，并广泛应用于临床。

3　抗 VEGF 辅助玻璃体切割术治疗 PDR 的有效性

PDR 患者眼部情况复杂，即使接受过规范的全视网膜激光光凝（panretinal photocoagulation，PRP），病情仍可继续进展，最终因大量视网膜新生血管形成、破裂出血，而致玻璃体积血（vitreous hemorrhage，VH），机化膜形成造成牵拉性视网膜脱离（tractional retina degeneration，TRD），严重威胁视力[32]。玻璃体切割术（pars plana vitrectomy，PPV）可清除 PDR 所引起的玻璃体积血，解除增殖膜对视网膜的牵拉，是治疗 PDR 的有效方法，同时清除了玻璃体腔内过高表达的多种促血管生成因子，一定程度缓解了视网膜的缺血缺氧状态，手术后 PDR 的进展往往能够得到控制[33]。手术成功与否及术后并发症的发生率与术前眼内 VEGF 浓度等多种因素相关。研究发现，PDR 患者眼部 VEGF 浓度与手术后早期玻璃体出血、虹膜新生血管的形成、远期视力预后及术后 PDR 进展均存在明显相关性：术前前房内 VEGF 浓度越高，则术后虹膜新生血管发生率越大，玻璃体腔内 VEGF 浓度越高，术后早期发生玻璃体再出血的风险越大，远期视力预后也越差；玻璃体腔内 VEGF 浓度每增加 100 pg/ml，PPV 后 PDR 继续进展的概率增加 1.5 倍[33-34]。

3.1　减少术中及术后并发症

PDR 患者视网膜缺血缺氧明显，导致视网膜水肿、脆性变

大，在处理机化膜时医源性视网膜破孔的发生率较高，并出现活动性出血而影响手术野的清晰度。如果在较严重活动性出血的情况下，继续进行气/液交换，由于血小板的残留，术后再次出现机化膜的概率非常高，另外还可出现前房出血、再次玻璃体积血以及视网膜表面出血。止血不彻底、巩膜切口处新生血管长入等是术后出血的主要来源[35]，严重影响患者术后视功能的恢复和远期预后。高达 75% 的患眼出现肉眼可见的术后玻璃体积血，再出血一般出现在术后早期(1 个月内)[36-37]。术后再出血患眼，即使出血能够自行吸收，仍然易出现视网膜表面机化膜，严重者可因机化膜收缩牵拉视网膜脱离而需再次手术。

PPV 前先行抗 VEGF 治疗可显著减少术中出血，降低术中医源性视网膜裂孔的发生率。Chen 等[38]首次将抗 VEGF 药物应用到 PDR 患者的 PPV 治疗中，发现术前 2 周玻璃体腔注射贝伐单抗，再行 PPV 可显著减少术中和术后出血，医源性并发症的发生率也大大降低。部分研究术中出血发生率甚至可降至 2.04%[39-44]；术后 1 个月内玻璃体出血的发生率也明显降低，并且出血在两周内即可自行吸收，与单纯 PPV 治疗的患眼相比，出血吸收时间可缩短一半以上，因再出血需要二次手术者也相应减少[42]。抗 VEGF 药物辅助 PPV 治疗 PDR 可将医源性裂孔的发生率降至 30% 以下[45-47]。近期中国 2 项研究发现，应用雷珠单抗辅助 PPV 可将医源性视网膜裂孔的发生率降至 9.37% 和 2%[48-49]。Pokroy 等[50]还发现，在复杂 TRD 的 PDR 患者中，术前玻璃体腔注射抗 VEGF 药物对于<40 岁的年轻 PDR 患者术后恢复和远期预后的受益更为明显。

由于抗 VEGF 药物的辅助，PDR 患者行 PPV 的难度得以降低，术中出血减少，手术时间、术中视网膜电凝的使用率、硅油填充比例均有下降，极大程度降低了手术创伤[39,44,45-48,51]。Rizzo 等[52]的前瞻对照研究发现，贝伐单抗辅助 PPV 治疗 11 眼，其中仅 2 例患者术中需电凝止血，平均手术时间为57 min，而单纯 PPV 治疗 11 眼，其中 9 眼术中需电凝止血，平均手术时间为 83 min，两者差异均有统计学意义。

微观层面，术中取剥离的机化膜做组织病理学和免疫组化研究发现，PPV 前 1 周注射贝伐单抗的患眼机化膜上新生血管数量、血管内皮细胞数、VEGF 表达均显著降低，但是抑制血管生成的色素上皮衍生因子(pigment epithelium-derived factor, PEDF)的表达不受影响[53]，再次印证了抗 VEGF 辅助 PPV 治疗 PDR 的可行性。

3.2　改善视力预后

由于缩短了手术时间，并降低了手术并发症的发生率，抗 VEGF 辅助 PPV 治疗的患眼术后视力恢复较快，且更早趋于稳定。Zaman 等[54]发现抗 VEGF 辅助 PPV 术后 6 个月 75% 的患眼最佳矫正视力可达 0.1 以上，83% 视力均有提高，视力下降者仅占 4%，而单纯 PPV 治疗者仅 46% 的患眼可恢复至 0.1 以上，53% 视力不能提高。Rizzo 等[52]发现贝伐单抗辅助 PPV，术后 6 个月患眼视力可由 1.87 logMAR 提高至 0.88 logMAR。

3.3　有效性影响因素

术前 1 周行抗 VEGF 药物玻璃体腔注射能够有效抑制新生血管活动，对于后续的 PPV 有较大帮助[39-41]。抗 VEGF 药物玻璃体腔注射后 24 h 即可发挥明显的生物学作用，对手术起到良好的辅助作用[43]。抗 VEGF 药物注药后 7 d 内对新生血管的抑制作用均较为明显，能够达到减少手术并发症的目的，且此时间段内没有机化膜过度增生的报道[55]。di Lauro 等[47]曾对 PDR 患者术前 1 周和 3 周抗 VEGF 药物玻璃体注药辅助 PPV 进行比较，发现 2 个组术中、术后并发症方面均较单纯 PPV 治疗组有显著优势，术前 1 周注药组术中出血、医源性视网膜破孔的发生率、术中电凝使用频率等均低于术前 3 周注药组。新生血管活跃的 PDR 患眼单次注射抗 VEGF 药物对新生血管的抑制作用及维持时间都极为有限，需多次重复注射或辅以 PRP、PPV 等才能抑制 PDR 的进展[56]。因此，对已发展至需要 PPV 干预的 PDR 患者，抗 VEGF 药物应用的真正优势在于在有限药物作用时间窗内实现其减少手术并发症和降低手术创伤的积极作用[57]。除术前注药外，Ahn 等[58]还发现手术结束时玻璃体腔注射贝伐单抗也可降低术后早期玻璃体出血的发生率，甚至较术前注药组作用更显著，其原理为对术中切断或潜在的新生血管起到收缩作用，并且在术后一段时间内持续抑制 VEGF，减少新生血管的生长，但该方法不能起到缩短手术时间、减少术中出血等作用。

不同抗 VEGF 药物对于手术的辅助作用大致相同。Pakzad-Vaezi 等[46]随机对照试验发现，术前 7 d 玻璃体腔注射雷珠单抗 0.5 mg 和贝伐单抗 1.25 mg 相比，术中及术后出血发生率、手术时间、视力预后等均无显著差异。Su 等[42]研究发现，术前 7 d 玻璃体腔注射康柏西普 0.5 mg，术中及术后并发症的发生率均可显著降低，其中术中出血发生率由 77.8% 降至 11.1%，电凝止血的应用率由 44.4% 降至 5.5%。

不同剂量的同一种抗 VEGF 药物玻璃体注药对 PPV 的辅助作用也大致相同，Hattori 等[20]发现 PPV 前 3 d 玻璃体腔分别注射 0.16、0.31、0.63 和 1.25 mg 贝伐单抗，玻璃体腔 VEGF 浓度均可显著降低，术中出血亦明显减少，但各组间差异无统计学意义。然而，重复注射或大剂量(2.5 mg)注射贝伐单抗有可能使黄斑中心凹无血管区面积扩大，导致黄斑水肿的发生[59]。因此临床上仍应避免大剂量或短期内频繁的玻璃体腔注射抗 VEGF 药物。表 1 为近年来部分应用抗 VEGF 药物辅助 PPV 治疗 PDR 的临床研究。

4　抗 VEGF 辅助 PPV 治疗 PDR 的安全性

抗 VEGF 对 PPV 的帮助得到广泛的肯定，但抗 VEGF 药物对眼部血管、血供的影响也应高度重视。在小鼠缺血损伤动物模型中，按照每周一次的频率玻璃体腔注射抗 VEGF 药物，6 周后小鼠视网膜神经节细胞发生不可逆损害[60]。同期的兔子模型显示，单次玻璃体腔内注射抗 VEGF 药物不会对神经节细胞造成损害[61]。Ushida 等[62]研究发现，PPV 前2～8 d玻璃体腔注射贝伐单抗的 PDR 患者，术后视网膜电图(electroretinogram, ERG)及视野检查结果均与单纯 PPV 组相似，而视网膜功能未出现明显异常，这可能是由于这部分患者仅行 1 次抗 VEGF 药物注射，且经过 PPV 后玻璃体腔药物浓度又会显著降低，因此

表 1　近年抗 VEGF 药物辅助 PPV 治疗 PDR 的临床研究

研究	年份	眼数	实验组	对照组	观察项目	结果
王德功等[49]	2015	100	IVR 0.5 mg(术前 3～4 d)+PPV	单纯 PPV	术中出血、电凝应用、医源性视网膜裂孔、器械交换次数、视网膜切开、手术时间	实验组均明显低于对照组
Su 等[42]	2016	36	IVC 0.5 mg(术前 7 d)+PPV	单纯 PPV	术中出血、电凝、医源性裂孔、硅油使用、手术时间、术后并发症	实验组均明显低于对照组
Manabe 等[43]	2015	66	IVB 0.16 mg(术前 1 d)+PPV	单纯 PPV	术中出血、电凝、VEGF 浓度 术后早期 VH	实验组均明显低于对照组
di Lauro 等[47]	2010	72	A:IVB 1.25 mg(术前 7 d)+PPV/ B:IVB 1.25 mg(术前 20 d)+PPV	单纯 PPV	术中出血、医源性裂孔、电凝、手术时间 术后并发症等	术后复发网脱发生率三组间无显著差异,余各项实验组均低于实验组,术中出血发生率 A 组显著低于 B 组
Pokroy 等[50]	2011	99	IVB 1.25 mg(术前 30 d 内)+PPV	单纯 PPV	术后 BCVA、并发症、手术时间	2 个组术后视力均有提高,实验组好于对照组
Rizzo 等[52]	2008	22	IVB 1.25 mg(术前 5-7 d)+PPV	单纯 PPV	术中出血、电凝应用、医源性视网膜裂孔、器械交换次数、视网膜切开、手术时间	实验组均明显低于对照组
Ahn 等[58]	2011	107	A:IVB 1.25 mg(术前 1～14 d)+PPV/ B:IVB 1.25 mg(手术结束前)+PPV	单纯 PPV	术后早期及晚期再出血发生率	实验组明显低于对照组,且再出血吸收更快;术后出血发生率 B 组低于 A 组
Pakzad-Vaezi 等[46]	2014	29	IVB 1.25 mg(术前 7 d)+PPV/ IVR 0.5 mg(术前 7 d)+PPV	-	术中出血、医源性裂孔、术后并发症等	2 个组间无显著差异
Hattori 等[20]	2010	52	IVB 0.16/0.31/0.63/1.25 mg(术前 3 d)+PPV	单纯 PPV	VEGF 浓度、术中出血	实验组各组 VEGF 浓度均显著降低

注:VEGF:血管内皮生长因子;PPV:玻璃体切割术;PDR:增生性糖尿病视网膜病变;IVR:玻璃体腔注射雷珠单抗;IVB:玻璃体腔注射贝伐单抗;IVC:玻璃体腔注射康柏西普;VH:玻璃体出血;BCVA:最佳矫正视力

应用抗 VEGF 药物辅助 PPV 治疗 PDR 不会对视网膜造成额外损伤。部分 PDR 患者注射抗 VEGF 药物后,机化膜不仅未软化消褪,反而加重,引起广泛的 TRD,使得后续手术难度增加[36,45]。Arevalo 等[63]对 211 眼 PDR 进行回顾研究,其中 11 眼(占 5.2%)玻璃体腔注射贝伐单抗后加重增殖膜牵拉视网膜,总结发现这部分患者均通过皮下注射胰岛素治疗糖尿病,且血糖控制不佳;患眼曾接受过 PRP 治疗但是病情继续进展;或术前已存在视网膜脱离。TRD 加重的时间多在注药 5 d 后,平均为注药 13 d 后。也有研究报道了类似的注药后纤维化加重的案例,可能是已存在的 TRD 因新生血管膜退化收缩而加重,或反复注射所致[64-65]。术中取患眼机化膜做免疫病理学研究发现,术前注射贝伐单抗的患眼,其机化膜中基质成分明显增多,同时膜上纤维组织也有一定增加,且有大量巨噬细胞包绕的类圆形结构,提示玻璃体腔注射贝伐单抗还是在一定程度上激发了机体的炎症反应;免疫组织化学也发现机化膜上 CTGF 的表达较对照组明显上调,视网膜表面机化膜上纤维收缩的成分亦有所增加,机化膜增生收缩,反而为后续的手术治疗造成困难[48,66]。在玻璃体注射抗 VEGF 药物与 PPV 间隔超过 2 周的 PDR 患眼中还发现,玻璃体腔内 VEGF 浓度显著下降,但碱性成纤维细胞生长因子(basic fibroblast growth factor, bFGF)浓度却明显升高,刺激玻璃体视网膜的增生和纤维化,而两者时间间隔为 5 d 的患者玻璃体内 bFGF 升高并不明显,提示如应用抗 VEGF 药物辅助 PPV 治疗严重的 PDR 患者,应严格控制两者时间间隔,警惕用药不当导致 PDR 加重[67]。

此外抗 VEGF 辅助 PPV 治疗 PDR 存在因玻璃体腔注药所带来的相关并发症,如眼压升高、眼内炎、视网膜脱离等,同样需要在治疗中按照相关操作规范严格控制。

抗 VEGF 药物的应用是当今医学界的热点,这也引发了诸多有关其单独应用或与激光、手术治疗联合用于治疗眼底相关疾病的探索。玻璃体腔注射抗 VEGF 药物辅助 PPV 对于玻璃体积血和重度 PDR 有较为肯定的疗效。但是 PPV 前多长时间玻璃体注射抗 VEGF 药物,注射次数,以及如何防止注药后 TRD 加重,仍然需要在大量随机对照试验中加以论证。

参考文献

[1] Guariguata L, Whiting DR, Hambleton I, et al. Global estimates of diabetes prevalence for 2013 and projections for 2035[J]. Diabetes Res Clin Pract, 2014, 103(2): 137-149. DOI: 10.1016/j.diabres.2013.11.002.

[2] Zhang X, Saaddine JB, Chou CF, et al. Prevalence of diabetic retinopathy in the United States, 2005-2008[J]. JAMA, 2010, 304: 649-656.

[3] Kyari F, Tafida A, Sivasubramaniam S, et al. Prevalence and risk factors for diabetes and diabetic retinopathy: results from the Nigeria national blindness and visual impairment survey[J/OL]. BMC Public Health, 2014, 14: 1299[2016-04-09]. https://bmcpublichealth.biomedcentral.com/articles/10.1186/1471-2458-14-1299. DOI: 10.1186/1471-2458-14-1299.

[4] Michaelson IC, Berman ER. New concepts on the pathogenesis of diabetic retinopathy[J]. Harefuah, 1983, 104(10): 463-464.

[5] Aiello LP, Avery RL, Arrigg PG, et al. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders[J]. N Engl J Med, 1994, 331(22): 1480-1487. DOI: 10.1056/NEJM199412013312203.

[6] Wang X, Wang G, Wang Y. Intravitreous vascular endothelial growth factor and hypoxia-inducible factor 1α in patients with proliferative diabetic retinopathy[J]. Am J Ophthalmol, 2009, 148(6): 883-889. DOI: 10.1016/j.ajo.2009.07.007.

[7] Chung EJ, Kang SJ, Koo JS, et al. Effect of intravitreal bevacizumab on vascular endothelial growth factor expression in patients with proliferative diabetic retinopathy[J]. Yonsei Med J, 2011, 52(1): 151-157. DOI: 10.3349/ymj.2011.52.1.151.

[8] Shibuya M. Differential roles of vascular endothelial growth factor

receptor-1 and receptor-2 in angiogenesis[J]. J Biochem Mol Biol, 2006, 39(5): 469-478.
[9] Kovacs K, Marra KV, Yu G, et al. Angiogenic and inflammatory vitreous biomarkers associated with increasing levels of retinal ischemia[J]. Invest Ophthalmol Vis Sci, 2015, 56(11): 6523-6530. DOI: 10.1167/iovs.15-16793.
[10] Klaassen I, van Geest RJ, Kuiper EJ, et al. The role of CTGF in diabetic retinopathy[J]. Exp Eye Res, 2015, 133: 37-48. DOI: 10.1016/j.exer.2014.10.016.
[11] Abu EAM, Alam K, Nawaz MI, et al. Upregulated expression of heparanase in the vitreous of patients with proliferative diabetic retinopathy originates from activated endothelial cells and leukocytes[J]. Invest Ophthalmol Vis Sci, 2015, 56(13): 8239-8247. DOI: 10.1167/iovs.15-18025.
[12] Jain A, Saxena S, Khanna VK, et al. Status of serum VEGF and ICAM-1 and its association with external limiting membrane and inner segment-outer segment junction disruption in type 2 diabetes mellitus[J]. Mol Vis, 2013, 19: 1760-1768.
[13] Li B, Sharpe EE, Maupin AB, et al. VEGF and PlGF promote adult vasculogenesis by enhancing EPC recruitment and vessel formation at the site of tumor neovascularization[J]. FASEB J, 2006, 20(9): 1495-1497. DOI: 10.1096/fj.05-5137fje.
[14] Adamiec-Mroczek J, Oficjalska-Młyńczak J. Assessment of selected adhesion molecule and proinflammatory cytokine levels in the vitreous body of patients with type 2 diabetes—role of the inflammatory-immune process in the pathogenesis of proliferative diabetic retinopathy[J]. Graefe's Arch Clin Exp Ophthalmol, 2008, 246(12): 1665-1670. DOI: 10.1007/s00417-008-0868-6.
[15] Wu SL, Zhan DM, Xi SH, et al. Roles of tissue plasminogen activator and its inhibitor in proliferative diabetic retinopathy[J]. Int J Ophthalmol, 2014, 7(5): 764-767. DOI: 10.3980/j.issn.2222-3959.2014.04.
[16] Saleem S, Azam A, Maqsood SI, et al. Role of ACE and PAI-1 polymorphisms in the development and progression of diabetic retinopathy[J/OL]. PLoS One, 2015, 10(12): e0144557[2016-6-20]. http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0144557. DOI: 10.1371/journal.pone.0144557.
[17] Rusnak S, Vrzalova J, Sobotova M, et al. The measurement of intraocular biomarkers in various stages of proliferative diabetic retinopathy using multiplex xMAP technology[J/OL]. J Ophthalmol, 2015, 2015: 424783[2015-5-28]. https://www.hindawi.com/journals/joph/2015/424783. DOI: 10.1155/2015/424783.
[18] Nishiguchi KM, Ushida H, Tomida D, et al. Age-dependent alteration of intraocular soluble heparan sulfate levels and its implications for proliferative diabetic retinopathy[J]. Mol Vis, 2013, 19: 1125-1131.
[19] Ma Y, Zhang Y, Zhao T, et al. Vascular endothelial growth factor in plasma and vitreous fluid of patients with proliferative diabetic retinopathy patients after intravitreal injection of bevacizumab[J]. Am J Ophthalmol, 2012, 153(2): 307-313.e2. DOI: 10.1016/j.ajo.2011.08.006.
[20] Hattori T, Shimada H, Nakashizuka H, et al. Dose of intravitreal bevacizumab (Avastin) used as preoperative adjunct therapy for proliferative diabetic retinopathy[J]. Retina, 2010, 30(5): 761-764. DOI: 10.1097/IAE.0b013e3181c70168.
[21] Willett CG, Boucher Y, di TE, et al. Direct evidence that the VEGF-specific antibody bevacizumab has antivascular effects in human rectal cancer[J]. Nat Med, 2004, 10(2): 145-147. DOI: 10.1038/nm988.
[22] Martin DF, Maguire MG, Fine SL, et al. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results[J]. Ophthalmology, 2012, 119(7): 1388-1398. DOI: 10.1016/j.ophtha.2012.03.053.
[23] Epstein DL, Algvere PV, von WG, et al. Bevacizumab for macular edema in central retinal vein occlusion: a prospective, randomized, double-masked clinical study[J]. Ophthalmology, 2012, 119(6): 1184-1189. DOI: 10.1016/j.ophtha.2012.01.022.
[24] Stein JD, Newman-Casey PA, Kim DD, et al. Cost-effectiveness of various interventions for newly diagnosed diabetic macular edema[J]. Ophthalmology, 2013, 120(9): 1835-1842. DOI: 10.1016/j.ophtha.2013.02.002.
[25] Osaadon P, Fagan XJ, Lifshitz T, et al. A review of anti-VEGF agents for proliferative diabetic retinopathy[J]. Eye (Lond), 2014, 28(5): 510-520. DOI: 10.1038/eye.2014.13.
[26] Wu B, Wu H, Liu X, et al. Ranibizumab versus bevacizumab for ophthalmic diseases related to neovascularisation: a meta-analysis of randomised controlled trials[J/OL]. PLoS One, 2014, 9(7): e101253[2016-05-03]. http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0101253. DOI: 10.1371/journal.pone.0101253.
[27] Papadopoulos N, Martin J, Ruan Q, et al. Binding and neutralization of vascular endothelial growth factor (VEGF) and related ligands by VEGF Trap, ranibizumab and bevacizumab[J]. Angiogenesis, 2012, 15(2): 171-185. DOI: 10.1007/s10456-011-9249-6.
[28] Zehetner C, Bechrakis NE, Stattin M, et al. Systemic counterregulatory response of placental growth factor levels to intravitreal aflibercept therapy[J]. Invest Ophthalmol Vis Sci, 2015, 56(5): 3279-3286. DOI: 10.1167/iovs.15-16686.
[29] Sarwar S, Clearfield E, Soliman MK, et al. Aflibercept for neovascular age-related macular degeneration[J/OL]. Cochrane Database Syst Rev, 2016, 2: CD011346[2016-5-15]. http://dx.doi.org/10.1002/14651858.CD011346.pub2. DOI: 10.1002/14651858.CD011346.pub2.
[30] Chan CK, Jain A, Sadda S, et al. Optical coherence tomographic and visual results at six months after transitioning to aflibercept for patients on prior ranibizumab or bevacizumab treatment for exudative age-related macular degeneration (an American Ophthalmological Society thesis)[J]. Trans Am Ophthalmol Soc, 2014, 112: 160-198.
[31] Lu X, Sun X. Profile of conbercept in the treatment of neovascular age-related macular degeneration[J]. Drug Des Devel Ther, 2015, 9: 2311-2320. DOI: 10.2147/DDDT.S67536.
[32] 黎晓新, 姜燕荣, 尹红, 等. 进展型增生性糖尿病视网膜病变玻璃体切割手术的价值与意义[J]. 中华眼底病杂志, 2001, 17(3): 171-174.
Li XX, Jiang YR, Yin H, et al. Evaluation of vitrectomy in advanced proliferative diabetic retinopathy[J]. Chin Ocular Fundus Dis, 2001, 17(3): 171-174.
[33] Wakabayashi Y, Usui Y, Okunuki Y, et al. Intraocular VEGF level as a risk factor for postoperative complications after vitrectomy for proliferative diabetic retinopathy[J]. Invest Ophthalmol Vis Sci, 2012, 53(10): 6403-6410. DOI: 10.1167/iovs.12-10367.
[34] Wang J, Chen S, Jiang F, et al. Vitreous and plasma VEGF levels as predictive factors in the progression of proliferative diabetic retinopathy after vitrectomy[J/OL]. PLoS One, 2014, 9(10): e110531[2016-04-05]. http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0110531. DOI: 10.1371/journal.pone.0110531.
[35] 惠延年. 糖尿病视网膜病变并发症的玻璃体手术治疗和手术并发症控制[J]. 中华眼底病杂志, 2007, 23(4): 231-233.
Hui YN. Vitrectomy for complications of diabetic retinopathy and control of surgical complications[J]. Chin J Ocular Fundus Dis, 2007, 23(4): 231-233.
[36] Oyakawa RT, Schachat AP, Michels RG, et al. Complications of vitreous surgery for diabetic retinopathy. I. Intraoperative complications[J]. Ophthalmology, 1983, 90(5): 517-521.
[37] Novak MA, Rice TA, Michels RG, et al. Vitreous hemorrhage after vitrectomy for diabetic retinopathy[J]. Ophthalmology, 1984, 91: 1485-1489.
[38] Chen E, Park CH. Use of intravitreal bevacizumab as a preoperative adjunct for tractional retinal detachment repair in severe proliferative diabetic retinopathy[J]. Retina, 2006, 26(6): 699-700. DOI: 10.1097/01.iae.0000225351.87205.69.
[39] Zhao LQ, Zhu H, Zhao PQ, et al. A systematic review and meta-analysis of clinical outcomes of vitrectomy with or without intravitreal bevaciźumab pretreatment for severe diabetic retinopathy[J]. Br J Ophthalmol, 2011, 95(9): 1216-1222. DOI: 10.1136/bjo.2010.189514.

[40] Martinez-Zapata MJ, Martí-Carvajal AJ, Solà I, et al. Anti-vascular endothelial growth factor for proliferative diabetic retinopathy [DB]. Cochrane Database Syst Rev, 2014, 24(11): CD008721. DOI: 10.1002/14651858.CD008721.

[41] Smith JM, Steel DH. Anti-vascular endothelial growth factor for prevention of postoperative vitreous cavity haemorrhage after vitrectomy for proliferative diabetic retinopathy (Review) [DB]. Cochrane Database Syst Rev, 2015, 7(8): CD008214. DOI: 10.1002/14651858.CD008214.

[42] Su L, Ren X, Wei H, et al. Intravitreal conbercept (KH902) for surgical treatment of sever proliferative diabetic retinopathy[J]. Retina, 2016, 36(5): 938-943. DOI: 10.1097/IAE.0000000000000900.

[43] Manabe A, Shimada H, Hattori T, et al. Randomized controlled study of intravitreal bevacizumab 0.16 MG injected one day before surgery for proliferative diabetic retinopathy[J]. Retina, 2015, 35(9): 1800-1807. DOI: 10.1097/IAE.0000000000000577.

[44] 解正高,陈放,朱俊,等. Ranibizumab 辅助的 23G 玻璃体切割术治疗严重增生性糖尿病视网膜病变的疗效及安全性评价[J]. 中华实验眼科杂志, 2015, 33(12): 1113-1117. DOI: 10.3760/cma.j.issn.2095-0160.2015.12.013.
Xie ZG, Cheng F, Zhu J, et al. Therapeutic effect and safety of 23G pars plana vitrectomy assisted by ranibizumab for severe proliferative diabetic retinopathy[J]. Chin J Exp Ophthalmol, 2015, 33(12): 1113-1117. DOI: 10.3760/cma.j.issn.2095-0160.2015.12.013.

[45] Li CR, Sun SG, Hong W. Effect of intravitreal bevacizumab injection before vitrectomy on proliferative diabetic retinopathy [J]. Int J Ophthalmol, 2010, 3(3): 261-263. DOI: 10.3980/j.issn.2222-3959.2010.03.19.

[46] Pakzad-Vaezi K, Albiani DA, Kirker AW, et al. A randomized study comparing the efficacy of bevacizumab and ranibizumab as pre-treatment for pars plana vitrectomy in proliferative diabetic retinopathy [J]. Ophthalmic Surg Lasers Imaging Retina, 2014, 45(6): 521-524. DOI: 10.3928/23258160-20141118-06.

[47] di Lauro R, de Ruggiero P, di Lauro R, et al. Intravitreal bevacizumab for surgical treatment of severe proliferative diabetic retinopathy[J]. Graefe's Arch Clin Exp Ophthalmol, 2010, 248(6): 785-791. DOI: 10.1007/s00417-010-1303-3.

[48] 冯萧萧,肖丽波,胡竹林,等. 单纯 23G 玻璃体切割手术与玻璃体腔注射抗血管内皮生长因子单克隆抗体 ranibizumab 联合 23G 玻璃体切割手术治疗增生型糖尿病视网膜病变对比观察[J]. 中华眼底病杂志, 2014, 30(2): 193-194. DOI: 10.3760/cma.j.issn.1005-1015.2014.02.017.

[49] 王德功,陈松,王昀,等. 玻璃体腔注射 ranibizumab 对增生性糖尿病视网膜病变微创玻璃体视网膜手术影响[J]. 中国实用眼科杂志, 2015, 33(5): 467-470. DOI: 10.3760/cma.j.issn.1006-4443.2015.05.006.
Wang DG, Chen S, Wang J, et al. The effect of intravitreal ranibizumab to microincision vitreoretinal surgery for proliferative diabetic retinopathy[J]. Chin J Pract Ophthalmol, 2015, 33(5): 467-470. DOI: 10.3760/cma.j.issn.1006-4443.2015.05.006.

[50] Pokroy R, Desai UR, Du E, et al. Bevacizumab prior to vitrectomy for diabetic traction retinal detachment[J]. Eye (Lond), 2011, 25(8): 989-997. DOI: 10.1038/eye.2011.149.

[51] Zhang ZH, Liu HY, Hernandez-Da MSE, et al. Vitrectomy with or without preoperative intravitreal bevacizumab for proliferative diabetic retinopathy: a meta-analysis of randomized controlled trials[J]. Am J Ophthalmol, 2013, 156(1): 106-115. DOI: 10.1016/j.ajo.2013.02.008.

[52] Rizzo S, Genovesi-Ebert F, Di BE, et al. Injection of intravitreal bevacizumab (Avastin) as a preoperative adjunct before vitrectomy surgery in the treatment of severe proliferative diabetic retinopathy (PDR)[J]. Graefe's Arch Clin Exp Ophthalmol, 2008, 246(6): 837-842. DOI: 10.1007/s00417-008-0774-y.

[53] 胡博杰,刘新玲,李筱荣,等. 糖尿病视网膜增殖膜应用抗 VEGF 因子后组织病理学观察[J]. 天津医药, 2010, 38(4): 297-299. DOI: 10.3969/j.issn.0253-9896.2010.04.014.
Hu BJ, Liu XL, Li XR, et al. Histopathologic observation on membrane in diabetic retinopathy after anti-VEGF gene treatment[J]. Tianjin Med J, 2010, 38(4): 297-299. DOI: 10.3969/j.issn.0253-9896.2010.04.014.

[54] Zaman Y, Rehman AU, Memon AF. Intravitreal Avastin as an adjunct in patients with proliferative diabetic retinopathy undergoing pars plana vitrectomy[J]. Pak J Med Sci, 2013, 29(2): 590-592.

[55] Ishikawa K, Honda S, Tsukahara Y, et al. Preferable use of intravitreal bevacizumab as a pretreatment of vitrectomy for severe proliferative diabetic retinopathy[J]. Eye (Lond), 2009, 23(1): 108-111. DOI: 10.1038/sj.eye.6702983.

[56] Chung EJ, Kang SJ, Koo JS, et al. Effect of intravitreal bevacizumab on vascular endothelial growth factor expression in patients with proliferative diabetic retinopathy[J]. Yonsei Med J, 2011, 52(1): 151-157. DOI: 10.3349/ymj.2011.52.1.151.

[57] Rosenfeld PJ, Moshfeghi AA, Puliafito CA. Optical coherence tomography findings after an intravitreal injection of bevacizumab (avastin) for neovascular age-related macular degeneration[J]. Ophthalmic Surg Lasers Imaging, 2005, 36(4): 331-335.

[58] Ahn J, Woo SJ, Chung H, et al. The effect of adjunctive intravitreal bevacizumab for preventing postvitrectomy hemorrhage in proliferative diabetic retinopathy[J]. Ophthalmology, 2011, 118(11): 2218-2226. DOI: 10.1016/j.ophtha.2011.03.036.

[59] Lee SJ, Koh HJ. Enlargement of the foveal avascular zone in diabetic retinopathy after adjunctive intravitreal bevacizumab (avastin) with pars plana vitrectomy[J]. J Ocul Pharmacol Ther, 2009, 25(2): 173-174. DOI: 10.1089/jop.2008.0092.

[60] Nishijima K, Ng YS, Zhong L, et al. Vascular endothelial growth factor-A is a survival factor for retinal neurons and a critical neuroprotectant during the adaptive response to ischemic injury[J]. Am J Pathol, 2007, 171(1): 53-67. DOI: 10.2353/ajpath.2007.061237.

[61] Iriyama A, Chen YN, Tamaki Y, et al. Effect of anti-VEGF antibody on retinal ganglion cells in rats[J]. Br J Ophthalmol, 2007, 91(9): 1230-1233. DOI: 10.1136/bjo.2007.117309.

[62] Ushida H, Kachi S, Asami T, et al. Influence of preoperative intravitreal bevacizumab on visual function in eyes with proliferative diabetic retinopathy[J]. Ophthalmic Res, 2013, 49(1): 30-36. DOI: 10.1159/000324135.

[63] Arevalo JF, Maia M, Flynn HW, et al. Tractional retinal detachment following intravitreal bevacizumab (Avastin) in patients with severe proliferative diabetic retinopathy[J]. Br J Ophthalmol, 2008, 92(2): 213-216. DOI: 10.1136/bjo.2007.127142.

[64] Papadopoulos N, Martin J, Ruan Q, et al. Binding and neutralization of vascular endothelial growth factor (VEGF) and related ligands by VEGF Trap, ranibizumab and bevacizumab[J]. Angiogenesis, 2012, 15(2): 171-185. DOI: 10.1007/s10456-011-9249-6.

[65] Moradian S, Ahmadieh H, Malihi M, et al. Intravitreal bevacizumab in active progressive proliferative diabetic retinopathy[J]. Graefe's Arch Clin Exp Ophthalmol, 2008, 246(12): 1699-1705. DOI: 10.1007/s00417-008-0914-4.

[66] El-Sabagh HA, Abdelghaffar W, Labib AM, et al. Preoperative intravitreal bevacizumab use as an adjuvant to diabetic vitrectomy: histopathologic findings and clinical implications[J]. Ophthalmology, 2011, 118(4): 636-641. DOI: 10.1016/j.ophtha.2010.08.038.

[67] Li JK, Wei F, Jin XH, et al. Changes in vitreous VEGF, bFGF and fibrosis in proliferative diabetic retinopathy after intravitreal bevacizumab[J]. Int J Ophthalmol, 2015, 8(6): 1202-1206. DOI: 10.3980/j.issn.2222-3959.2015.06.22.

(收稿日期:2016-10-16)

(本文编辑:尹卫靖　杜娟)