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雷珠单抗联合视网膜激光光凝术对 BRVO 继发黄斑水肿患者视网膜电图 P1 波及生活质量的影响 *

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摘要 目的:探讨雷珠单抗联合视网膜激光光凝术对视网膜分支静脉阻塞(BRVO)继发黄斑水肿患者视网膜电图 P1 波及生活质量的影响。**方法:**选取 2017 年 1 月~2019 年 8 月期间我院收治的 BRVO 继发黄斑水肿患者 60 例,根据随机数字表法分为对照组(n=30)和研究组(n=30),对照组患者予以雷珠单抗治疗,研究组则在对照组的基础上联合视网膜激光光凝术治疗,比较两组患者疗效、视网膜电图 P1 波、生活质量及不良反应。**结果:**研究组治疗后 6 个月的临床总有效率为 93.33%(28/30),高于对照组的 70.00%(21/30)($P<0.05$)。两组患者治疗后 1 个月、治疗后 3 个月、治疗后 6 个月健康调查简表(SF-36)评分均升高,且研究组高于对照组($P<0.05$)。两组治疗后 6 个月视力升高,黄斑中心视网膜厚度(CMT)、眼压降低($P<0.05$);研究组治疗后 6 个月视力高于对照组,CMT、眼压低于对照组($P<0.05$)。研究组治疗后 6 个月 1 环、2 环、3 环的 P1 波振幅密度高于对照组($P<0.05$);而 1 环、2 环、3 环的 P1 波潜伏期低于对照组($P<0.05$)。两组不良反应发生率对比无差异($P>0.05$)。**结论:**BRVO 继发黄斑水肿患者经视网膜激光光凝术联合雷珠单抗治疗后,疗效显著,可有效提高视力及生活质量,改善黄斑水肿及病变区域的视网膜功能,且不增加不良反应发生率。

关键词:雷珠单抗;视网膜激光光凝术;视网膜分支静脉阻塞;黄斑水肿;视网膜电图 P1 波;生活质量

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The Effect of Laser Photocoagulation Combined with Ranibizumab on Electroretinogram P1 and Quality of Life in Patients with Macular Edema Secondary to Branch Retinal Vein Occlusion*

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ABSTRACT Objective: To investigate the effect of laser photocoagulation combined with ranibizumab on the electroretinogram P1 and quality of life in patients with macular edema secondary to branch vein occlusion (BRVO). **Methods:** From January 2017 to August 2019, 60 patients with macular edema secondary to BRVO in our hospital were selected, they were divided into control group (n=30) and study group (n=30) according to the method of random number table. Patients in the control group were treated with ranibizumab, while those in the study group were treated with retinal laser photocoagulation on the basis of the control group. The efficacy, P1 wave of electroretinogram, quality of life and adverse reactions of the two groups were compared. **Results:** The total clinical effective rate of the study group was 93.33% (28/30), which was higher than 70.00% (21/30) of the control group ($P<0.05$). The scores of health survey summary (SF-36) of the two groups were increased at 1 month after treatment, 3 months after treatment and 6 months after treatment, and those of the study group were higher than those of the control group ($P<0.05$). 6 months after treatment, the visual acuity of the two groups increased, and macular central retinal thickness (CMT) and intraocular pressure decreased ($P<0.05$). The visual acuity of the study group at 6 months after treatment was higher than that of the control group, and CMT and intraocular pressure were lower than those of the control group ($P<0.05$). 6 months after treatment, the P1 wave amplitude density of the 1st, 2nd and 3rd rings in the study group were higher than those of the control group ($P<0.05$), while the P1 wave latency of the 1st, 2nd and 3rd rings were lower than those of the control group ($P<0.05$). There was no significant difference in the incidence of adverse reactions between the two groups ($P>0.05$). **Conclusion:** Ranibizumab combined with retinal laser photocoagulation is effective in the treatment of macular edema secondary to BRVO, which can effectively improve vision and quality of life, improve macular edema, and do not increase the incidence of adverse reactions.

Key words: Ranibizumab; Retinal laser photocoagulation; Branch retinal vein occlusion; Macular edema; P1 wave of electroretinogram; Quality of life

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前言

视网膜分支静脉阻塞 (Branch retinal vein occlusion, BRVO) 是临床常见的眼底血管病, 主要由静脉阻塞引发, 常继发黄斑水肿而导致患者视力下降, 给患者生活质量带来了严重影响^[1,2]。雷珠单抗是临床治疗此病的常用药物, 但此类治疗方案仍存在一定不足, 由于雷珠单抗半衰期短, 需多次、反复注射, 不仅会加重患者的疼痛, 还会增加玻璃体腔感染风险^[3-5]。视网膜激光光凝术也是治疗 BRVO 继发黄斑水肿的常用方法, 其可通过改善视网膜缺血及缺氧状态, 促进黄斑水肿及出血吸收, 进而发挥治疗效果^[6-8], 但长期的临床实践发现, 部分患者在接受此方案单独治疗后视力改善效果有限, 尚不能达到理想的治疗效果。鉴于此, 本研究通过探讨雷珠单抗联合视网膜激光光凝术对 BRVO 继发黄斑水肿患者视网膜电图 P1 波及生活质量的影响, 以期为临床治疗 BRVO 继发黄斑水肿提供数据支持, 现整理如下。

1 资料与方法

1.1 一般资料

选取 2017 年 1 月~2019 年 8 月期间我院收治的 BRVO 继发黄斑水肿患者 60 例, 纳入标准: (1) 经光学相干断层扫描确诊; (2) 患者及其家属知情本研究且签署同意书; (3) 病程不超过 3 个月; (4) 符合雷珠单抗联合激光光凝术治疗适应证者; (5) 均为单眼发病者。排除标准: (1) 合并白内障、青光眼等眼科疾病者; (2) 合并糖尿病患者; (3) 合并心肝肾等脏器功能障碍者; (4) 合并精神障碍者; (5) 既往具有内眼手术、视网膜激光光凝术治疗史者。根据随机数字表法分为对照组 ($n=30$) 和研究组 ($n=30$), 其中对照组男 12 例, 女 18 例, 病程 1~3 月, 平均 (2.06 ± 0.37) 月; 年龄 41~69 岁, 平均 (52.67 ± 4.68) 岁; 患眼部位: 左眼 14 例, 右眼 16 例; 阻塞部位: 颞上分支 12 例, 颞下分支 18 例。研究组男 14 例, 女 16 例, 病程 0.8~3 月, 平均 (1.98 ± 0.42) 月; 年龄 39~68 岁, 平均 (51.98 ± 5.06) 岁; 患眼部位: 左眼 12 例, 右眼 18 例; 阻塞部位: 颞上分支 10 例, 颞下分支 20 例。两组患者一般资料对比未见统计学差异 ($P>0.05$), 具有可比性, 且此次研究已获取我院伦理学委员会批准。

1.2 方法

两组患者入院后均行常规检查, 初步确定 BRVO 继发黄斑水肿等情况。对照组给予玻璃体腔注射雷珠单抗 (Novartis Pharma Stein AG, 批准文号: S20170003, 规格: 10 mg/mL, 每瓶装量 0.20 mL) 治疗。治疗前 3 d 给予盐酸左氧氟沙星滴眼液 (参天制药株式会社, 国药准字 J20150106, 规格: 5 mL:24.4 mg) 5 g/L 滴眼, 注射雷珠单抗前冲洗结膜囊与泪道。注射时患者仰

卧, 采用盐酸奥布卡因滴眼液 (Santen Pharmaceutical Co., Ltd., 国药准字 J20160094, 规格: 20 mL:80 mg) 进行局部麻醉, 麻醉生效后常规消毒、铺巾。对患者前房进行穿刺, 放液 0.1 mL, 于患眼颞下象限角膜缘 3.5~4.0 mm 睫状体平坦部位处进针, 向玻璃体内注入 0.05 mL/0.5 mg 雷珠单抗, 注射完毕拔针。研究组则在对照组治疗的基础上治疗 1 周后实施视网膜激光光凝术治疗。治疗前 5 min, 采用盐酸奥布卡因滴眼液进行局部麻醉。放置全视网膜接触镜, 采用 532 激光机 (法国光太公司) 对患者进行治疗, 相关参数如下, 激光能量 90~120 mW, 光斑 50~100 μm , 曝光时间 0.1~0.2 s。

1.3 观察指标

(1) 两组均采用门诊复查的形式随访 6 个月, 统计两组治疗后 6 个月的疗效。疗效判定标准如下^[9]: 显效: 视力明显提升, 患者视网膜出血吸收良好, 荧光素眼底血管造影 (Fundus fluorescein angiography, FFA) 未见无灌注区与视网膜新生血管、荧光素渗漏; 有效: 视力轻度提升, 视网膜出血有所吸收, FFA 显示无灌注区与视网膜新生血管、荧光素渗漏有所改善; 无效: 视网膜出血无明显吸收, 视力未见改善, FFA 显示无灌注区与视网膜新生血管、荧光素渗漏无明显改善或恶化。总有效率 = 显效率 + 有效率。(2) 于治疗前、治疗后 1 个月、治疗后 3 个月、治疗后 6 个月采用健康调查简表 (SF-36)^[10] 评估两组生活质量, 总分 0~100 分, 分数越高生活质量越高。(3) 比较两组的治疗安全性。统计并记录两组白内障、一过性眼压增高、结膜下出血、角膜上皮擦伤及视网膜脱落等发生情况。(4) 记录两组患者治疗前、治疗后 6 个月的视力、黄斑中心视网膜厚度 (Macular central retinal thickness, CMT)、眼压情况, 其中视力采用国际通用标准 Snellen 视力表测定; 眼压采用眼压测定仪进行测定; CMT 采用光学相干断层扫描进行测量。(5) 于治疗前、治疗后 6 个月采用罗兰公司生产的 mfERG 检查仪及系统检测两组患者的 1 环 (视野半径 2.2 度)、2 环 (视野半径 9.42 度)、3 环 (视野半径 16.19 度) 的 P1 波振幅密度、P1 波潜伏期。

1.4 统计学方法

采用 SPSS 24.0 软件对数据进行统计分析。计数资料以例数或率表示, 采用卡方检验。计量资料以 $(\bar{x} \pm s)$ 表示, 采用 t 检验。 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 两组疗效比较

随访 6 个月, 本研究无失访病例。研究组治疗后 6 个月的临床总有效率为 93.33% (28/30), 高于对照组的 70.00% (21/30) ($P<0.05$); 详见表 1。

表 1 两组疗效比较 [例 (%)]

Table 1 Comparison of efficacy between the two groups [n (%)]

Groups	Markedly effective	Valid	Invalid	Total effective rate
Control group ($n=30$)	7 (23.33)	14 (46.67)	9 (30.00)	21 (70.00)
Study group ($n=30$)	12 (40.00)	16 (53.33)	2 (6.67)	28 (93.33)
χ^2				5.456
P				0.020

2.2 两组生活质量比较

两组患者治疗前 SF-36 评分比较无差异($P>0.05$);两组患

者治疗后 1 个月、治疗后 3 个月、治疗后 6 个月 SF-36 评分均升高,且研究组高于对照组($P<0.05$);详见表 2。

表 2 两组生活质量比较($\bar{x} \pm s$, 分)

Table 2 Comparison of quality of life between the two groups($\bar{x} \pm s$, scores)

Groups	Before treatment	1 month after treatment	3 months after treatment	6 months after treatment
Control group(n=30)	41.87± 5.22	63.71± 5.26 ^a	72.68± 8.71 ^{ab}	83.02± 9.57 ^{abc}
Study group(n=30)	41.26± 6.20	71.60± 6.17 ^a	80.62± 9.74 ^{ab}	90.11± 8.47 ^{abc}
t	0.412	5.330	3.328	3.467
P	0.682	0.000	0.002	0.001

Notes: compared with before treatment, ^a $P<0.05$; compared with 1 month after treatment, ^b $P<0.05$; compared with 3 months after treatment, ^c $P<0.05$.

2.3 两组视力、CMT、眼压情况

两组治疗前视力、CMT、眼压比较差异无统计学意义($P>0.05$);两组治疗后 6 个月视力升高,CMT、眼压降低($P<0.05$);研

究组治疗后 6 个月视力高于对照组,CMT、眼压低于对照组($P<0.05$);详见表 3。

表 3 两组视力、CMT、眼压情况($\bar{x} \pm s$)

Table 3 Visual acuity, CMT and intraocular pressure of the two groups($\bar{x} \pm s$)

Groups	Visual acuity		CMT(μ m)		Intraocular pressure(mmHg)	
	Before treatment	6 months after treatment	Before treatment	6 months after treatment	Before treatment	6 months after treatment
Control group(n=30)	0.53± 0.17	1.08± 0.29 ^a	580.34± 35.92	337.62± 24.88 ^a	16.34± 2.21	13.23± 2.64 ^a
Study group(n=30)	0.58± 0.16	1.33± 0.25 ^a	567.77± 36.89	215.78± 23.74 ^a	16.29± 2.78	10.21± 2.88 ^a
t	1.173	3.576	1.337	19.406	0.077	15.638
P	0.246	0.001	0.186	0.000	0.936	0.000

Note: compared with before treatment, ^a $P<0.05$.

2.4 两组视网膜电图 P1 波比较

两组患者治疗前 1 环、2 环、3 环的 P1 波振幅密度、P1 波潜伏期比较差异无统计学意义($P>0.05$);两组患者治疗后 6 个

月 1 环、2 环、3 环的 P1 波振幅密度均升高,且研究组高于对照组($P<0.05$);研究组治疗后 6 个月 1 环、2 环、3 环的 P1 波潜伏期均下降,且低于对照组($P<0.05$);详见表 4。

表 4 两组视网膜电图 P1 波比较($\bar{x} \pm s$)

Table 4 Comparison of P1 wave of electroretinogram between the two groups($\bar{x} \pm s$)

Groups	Time	P1 wave amplitude density(nV/deg ²)			P1 wave latency(ms)		
		1 ring	2 rings	3 rings	1 ring	2 rings	3 rings
Control group(n=30)	Before treatment	42.20± 11.35	35.33± 3.27	17.31± 2.28	42.19± 3.36	40.41± 2.29	39.37± 2.22
	6 months after treatment	57.98± 8.29 ^a	39.75± 4.81 ^a	21.84± 2.29 ^a	41.59± 3.25	39.96± 2.35	38.59± 2.31
Study group(n=30)	Before treatment	42.08± 9.32	35.07± 4.34	17.19± 1.29	42.23± 3.32	39.38± 2.34	39.42± 3.31
	6 months after treatment	71.08± 13.21 ^{ab}	44.23± 5.28 ^{ab}	24.15± 2.19 ^{ab}	36.93± 3.35 ^{ab}	35.03± 3.27 ^{ab}	34.15± 3.29 ^{ab}

Notes: compared with before treatment, ^a $P<0.05$; compared with control group, ^b $P<0.05$.

2.5 两组安全性比较

对照组治疗后发生白内障 1 例,一过性眼压增高 2 例,结膜下出血 1 例,视网膜脱落 1 例,不良反应发生率为 16.67%(5/30);研究组治疗后发生一过性眼压增高 1 例,结膜下出血 1 例,视网膜脱落 1 例,不良反应发生率为 10.00%(3/30);两组不良反应发生率比较无差异($\chi^2=1.176, P=0.278$)。

3 讨论

BRVO 是由多种因素共同引起的一种临床症候群,目前有关其确切的发病机制尚不十分明确,多数学者认为其与视网膜动脉供血不足有关,当视网膜动脉供血不足时,视网膜血液灌注减少,引起视网膜缺氧,进而导致视力下降^[1]。随着 BRVO 的病情进展,可于发病后数月产生黄斑水肿、新生血管性青光眼、

视网膜出血等严重并发症^[12]。其中黄斑水肿在 BRVO 中的发生率为 20%，会造成患者视力急剧下降，严重影响患者生活质量。黄斑水肿的发生机制和血-视网膜屏障的破坏有关，由于黄斑区血流灌注的减少以及毛细血管内压力增加，导致毛细血管内皮细胞肌膜连接受损，血管生成因子表达增加，渗出液增多，进而引起黄斑水肿的发生，且长期的黄斑水肿还可造成不可逆性的视功能损害^[13-15]。抗血管内皮生长因子(Vascular endothelial growth factor, VEGF)药物在治疗 BRVO 继发黄斑水肿中具有较好的临床疗效，雷珠单抗是第二代抗 VEGF 药物，穿透视网膜能力强，在玻璃体内可发挥较好的生物利用度，可有效抑制黄斑水肿，进而改善患者临床症状^[16-18]。但雷珠单抗也存在半衰期短，需多次注射等缺陷，给患者带来巨大的经济负担及精神压力^[19,20]。视网膜激光光凝术也是治疗 BRVO 继发黄斑水肿的主要方法之一，其可通过高温粘连色素上皮层、神经上皮层，有效避免视网膜的脱落^[21-23]。然而视网膜激光光凝术也会在一定程度上影响视网膜功能，且黄斑区域一般只能进行 1 次激光光凝治疗。

本次研究显示研究组的临床总有效率高于对照组，视力、眼压、CMT 及生活质量的改善情况均优于对照组，可见联合治疗方案治疗 BRVO 继发黄斑水肿，疗效显著，可有效减轻黄斑水肿，改善视力，并进一步提高生活质量。分析原因，雷珠单抗可通过抑制新生血管生成，实现血-视网膜屏障的调控，同时还可降低血管通透性，促进视网膜内渗液吸收，减轻黄斑水肿^[24,25]。激光光凝术的主要作用机制在于通过激光的热效应降低病变区域的视网膜耗氧量，进一步缓解视网膜无灌注区域的缺血缺氧状况；此外激光光凝术还可减少血液回流，进而缓解黄斑水肿，改善患者视力状况^[26,27]。雷珠单抗可弥补单独应用激光光凝术对 BRVO 继发黄斑水肿改善不足的缺陷，而激光光凝术可弥补雷珠单抗的多次注射缺陷，两者发挥协同作用，加速血-视网膜屏障功能恢复，有利于氧分由脉络膜渗透至视网膜内层，改善黄斑功能，提升视力，促进患者早日恢复正常生活及工作，患者的身心负担减少，社会参与感增强，生活质量进一步提升^[28]。P1 波振幅密度、P1 波潜伏期均是临床用于反映视网膜功能的指标，其中 P1 波潜伏期的长短与血管疾病严重程度呈正相关。本研究结果中研究组治疗后 6 个月 1~3 环的 P1 波振幅密度高于对照组，而 P1 波潜伏期则低于对照组，提示雷珠单抗联合视网膜激光光凝术治疗可有效改善患者视网膜功能。这可能与联合治疗可缓解视网膜缺血缺氧状况，促进视网膜循环进而改善视网膜功能有关^[29]。另两组不良反应发生率比较未见差异，可见该联合方案安全可靠，与既往^[30]研究报道结果基本一致。

综上所述，BRVO 继发黄斑水肿患者经视网膜激光光凝术联合雷珠单抗治疗后，可有效提高视力及生活质量，改善黄斑水肿及病变区域的视网膜功能，且安全性较好。

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(上接第 287 页)

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