



# 视网膜分支静脉阻塞继发黄斑水肿玻璃体腔注射康柏西普联合视网膜激光光凝治疗后中心凹视网膜厚度对远期视力预后的影响

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**【摘要】目的** 观察视网膜分支静脉阻塞 (BRVO) 继发黄斑水肿 (ME) 玻璃体腔注射康柏西普联合视网膜激光光凝治疗后黄斑中心凹视网膜厚度 (CMT) 对远期视力预后的影响。**方法** 回顾性非随机对照研究。临床检查确诊的缺血型BRVO继发ME患者41例41只眼纳入研究。其中, 男性23例23只眼, 女性18例18只眼。平均年龄 (56.49±8.94) 岁。均行最佳矫正视力 (BCVA)、光相干断层扫描检查。BCVA统计时换算为最小分辨角对数 (logMAR) 视力。患眼平均logMAR BCVA为0.82±0.41; 平均CMT为 (512.61±185.32) μm。依据治疗后1个月时CMT降低值将患眼分为无应答组、应答组, 分别为15例15只眼、26例26只眼。两组患者年龄、性别构成比较, 差异无统计学意义 ( $t=-0.298$ 、 $-1.708$ ,  $P=0.767$ 、 $0.096$ ); 注药次数比较, 差异有统计学意义 ( $t=3.589$ ,  $P=0.010$ ); 患眼平均logMAR BCVA、CMT比较, 差异无统计学意义 ( $t=2.056$ 、 $-1.876$ ,  $P=0.460$ 、 $0.070$ )。平均随访时间8个月。将随访时间≥6个月时的logMAR BCVA定义为远期视力。观察两组患眼治疗后1、6个月CMT和远期视力变化。Pearson相关性分析远期视力与年龄、治疗前logMAR BCVA、治疗前CMT、注药次数、治疗后1个月CMT降低值的相关性。多元回归分析远期视力与年龄、性别、治疗前logMAR BCVA、治疗前CMT、注药次数、治疗后1个月CMT降低值、椭圆体带完整性、外界膜 (ELM) 完整性的相关性。**结果** 治疗后1个月, 患眼CMT较治疗前降低 (231.48±177.99) μm; ELM、椭圆体带平均完整性分别为0.56±0.50、0.41±0.50。治疗后6个月, 患眼平均logMAR BVCA为0.48±0.34。Pearson相关性分析结果显示, 远期视力与治疗前logMAR BCVA以及治疗后1个月CMT降低值、注药次数呈正相关 ( $P<0.05$ ); 与年龄、治疗前CMT无相关 ( $P>0.05$ )。多元回归分析结果显示, 远期视力与治疗前logMAR BVCA、治疗后1个月CMT降低值、ELM完整性、注药次数相关 ( $P<0.05$ ); 与年龄、性别、治疗前CMT、椭圆体带完整性无相关 ( $P>0.05$ )。治疗后6个月, 无应答组、应答组患眼logMAR BCVA分别为0.86±0.23、0.26±0.14; 平均CMT分别为 (398.93±104.87)、(255.15±55.18) μm; 平均注药次数分别为 (2.53±1.46)、(1.31±0.74) 次。两组患眼平均logMAR BCVA、CMT、注药次数比较, 差异均有统计学意义 ( $t=10.293$ 、 $5.773$ 、 $3.589$ ,  $P=0.000$ 、 $0.000$ 、 $0.001$ )。所有患者均未出现与药物、玻璃体腔注射相关的并发症。**结论** 缺血型BRVO继发ME玻璃体腔注射康柏西普联合视网膜激光光凝治疗后远期视力与治疗后1个月CMT降低值、外界膜完整性相关; 与治疗前CMT、椭圆体带完整性无相关。

**【关键词】** 视网膜静脉闭塞/治疗; 黄斑水肿/治疗; 血管生成抑制剂/治疗应用; 激光凝固术; 体层摄影术, 光学相干

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**The effect of retinal thickness on the prognosis of long-term vision after the treatment of intravitreal injection of Conbercept combined with retinal laser photocoagulation for macular edema secondary to branch retinal vein occlusion** Liu Penghui, Meng Xuxia, Zhou Xianhui  
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**【Abstract】Objective** To observe the effect of macular retinal thickness (CMT) on the long-term visual prognosis after intravitreal injection of Conbercept combined with retinal laser photocoagulation for macular

edema (ME) secondary to branch retinal vein occlusion (BRVO). **Methods** A retrospective non randomized controlled study. Forty-one patients (41 eyes) of ischemic BRVO secondary ME were included in the study. Among them, there were 23 males (23 eyes) and 18 females (18 eyes). The average age was  $(56.49 \pm 8.94)$  years. The best corrected visual acuity (BCVA) and optical coherence tomography were performed. The mean logMAR BCVA was  $0.82 \pm 0.41$ , and the mean CMT was  $(512.61 \pm 185.32)$   $\mu\text{m}$ . According to the CMT reduction value at 1 month after treatment, the eyes were divided into no response group and response group, each has 15 patients of 15 eyes and 26 patients of 26 eyes respectively. The age and sex composition of the two groups were not statistically significant ( $t=-0.298, -1.708; P=0.767, 0.096$ ), and the difference of frequency of injection was statistically significant ( $t=3.589, P=0.010$ ), and there was no statistical difference between the patients with logMAR BCVA and CMT ( $t=2.056, -1.876; P=0.460, 0.070$ ). The average follow-up was 8 months. The logMAR BCVA on 6 months after treatment was defined as long term vision. The changes of long term vision and CMT on 1 and 6 months of two groups after treatment were observed. Pearson correlation analysis showed that the correlation between long-term vision and age, logMAR BCVA before treatment, CMT before treatment, frequency of injection, and CMT value decreased 1 month after treatment. The correlation of long-term visual acuity with age, sex, logMAR BCVA before treatment, CMT before treatment, number of drugs before treatment, CMT reduction at 1 month after treatment, integrity of ellipsoid band and integrity of external membrane (ELM) were analyzed by multiple regression analysis. **Results** On 1 month after treatment, the CMT of the eyes was lower than that before treatment ( $231.48 \pm 177.99$ )  $\mu\text{m}$ , and the average integrity of ELM and ellipsoid were  $0.56 \pm 0.50$  and  $0.41 \pm 0.50$  respectively. On 6 months after treatment, the average logMAR BVCA of the eyes was  $0.48 \pm 0.34$ . The results of Pearson correlation analysis showed that the long-term vision was positively correlated with the logMAR BCVA before treatment and the number of CMT reduction and the number of drug injection at 1 month after treatment ( $P < 0.05$ ); there was no correlation with age and CMT before treatment ( $P > 0.05$ ). The results of multiple regression analysis showed that the long-term vision was associated with logMAR BVCA before treatment, CMT reduction, ELM integrity, and the number of times of injection ( $P < 0.05$ ), and no correlation with age, sex, CMT before treatment and the integrity of the ellipsoid ( $P > 0.05$ ). On the 6 months after treatment, the logMAR BCVA in the non-response group and the response group were  $0.86 \pm 0.23$  and  $0.26 \pm 0.14$ , and the average CMT was respectively ( $398.93 \pm 104.87$ ) and ( $255.15 \pm 55.18$ )  $\mu\text{m}$ , and the average injection times were respectively ( $2.53 \pm 1.46$ ) and ( $1.31 \pm 0.74$ ) times. The average logMAR BCVA, CMT and injection times of the two groups were statistically significant ( $t=10.293, 5.773, 3.589; P=0.000, 0.000, 0.001$ ). No complications related to drug or intravitreal injection occurred in all patients. **Conclusion** The long-term vision of ME secondary to BRVO after intravitreal injection of Conbercept combined with retinal laser photocoagulation was associated with the decrease of CMT and the integrity of the ELM after 1 month of treatment, no correlation was found between CMT and ellipsoid integrity before treatment.

**【Key words】** Retinal vein occlusion/therapy; Macular edema/therapy; Angiogenesis inhibitors/therapeutic use; Laser coagulation; Tomography, optical coherence

视网膜分支静脉阻塞 (BRVO) 继发黄斑水肿 (ME) 的黄斑格栅样激光光凝治疗可减少血管渗漏、减轻 ME, 但视力提高有限且存在损伤视功能风险<sup>[1]</sup>。玻璃体腔注射抗血管内皮生长因子 (VEGF) 药物可有效治疗 BRVO<sup>[2]</sup>, 联合激光光凝治疗较单一玻璃体腔注射抗 VEGF 药物治疗的疗效更好<sup>[3-6]</sup>。但治疗后 ME 仍易复发或持续存在, 需多次重复治疗<sup>[7,8]</sup>, 且部分患者多次重复治疗后可出现耐药等情况<sup>[9]</sup>。为此, 本研究对康柏西普联合视网膜激光光凝治疗后 1 个月时的黄斑形态变化进行了观察, 初步探讨其与远期视力预后的关系。

## 1 对象和方法

回顾性非随机对照研究。本研究遵循赫尔辛基宣

言; 经青岛大学附属医院伦理委员会审核批准; 所有患者均获知情并签署同意书。

2015 年 12 月至 2016 年 12 月在我院检查确诊的缺血型 BRVO 继发 ME 患者 41 例 41 只眼纳入研究。其中, 男性 23 例 23 只眼, 女性 18 例 18 只眼; 均为单眼。年龄 41~76 岁, 平均年龄 ( $56.49 \pm 8.94$ ) 岁。纳入标准: (1) 视网膜颞上或颞下分支静脉阻塞继发 ME; (2) 荧光素眼底血管造影 (FFA) 检查显示视网膜毛细血管无灌注区  $> 5$  个视盘直径<sup>[10]</sup>; (3) 光相干断层扫描 (OCT) 检查可见黄斑凹陷消失或隆起, 视网膜呈弥漫性增厚; (4) 高血压患者内科系统治疗, 血压  $< 140/90$  mm Hg ( $1 \text{ mmHg}=0.133 \text{ kPa}$ ); (5) 病程  $<$

3个月。排除标准：(1)既往接受过玻璃体腔注射抗VEGF药物或结膜下注射曲安奈德者；(2)既往接受过激光光凝治疗者；(3)确诊或怀疑浅前房、青光眼或高血压者；(4)ME继发于老年性黄斑变性、糖尿病视网膜病变、视网膜静脉周围炎、视网膜血管炎者；(5)除BRVO外其他眼部疾病者；(6)有药物过敏史以及支气管哮喘、糖尿病患者。

均行最佳矫正视力(BCVA)、OCT、眼底彩色照相、FFA检查。BCVA检查采用标准对数视力表,统计时换算为最小分辨角对数(logMAR)视力;眼底彩色照相采用日本Kowa nonmyd  $\alpha$ -D III免散瞳眼底照相机;FFA检查采用德国Heidelberg公司Spectralis HRA。患眼平均logMAR BCVA为 $0.82 \pm 0.41$ 。

OCT检查采用德国Heidelberg公司Spectralis OCT仪。以黄斑中心凹为中心,采用水平线性扫描,扫描深度1.9 mm,扫描面积 $6 \text{ mm} \times 6 \text{ mm}$ ,横向分辨率 $14 \mu\text{m}$ ,轴向分辨率 $7 \mu\text{m}$ ,扫描模式 $512 \times 496$ 。应用仪器自带测距软件测量视网膜神经上皮层内界膜至视网膜色素上皮层强反光带外侧的距离,并以此作为黄斑中心凹视网膜厚度(CMT)。测量由两名经验丰富的技师完成,重复测量3次,取平均值<sup>[11]</sup>。观察灰度图经中心水平扫描线上、中心 $500 \mu\text{m}$ 范围内黄斑区椭圆体带、外界膜(ELM)反射光带完整性。椭圆体带、外界膜完整性分为存在和缺失。存在:光带信号连续光滑,以1表示;缺失:光带信号部分或完全中断,以0表示<sup>[12]</sup>。患眼平均CMT为 $(512.61 \pm 185.32) \mu\text{m}$ 。

玻璃体腔注射康柏西普(IVR)按常规操作完成。以1 ml注射器抽取 $10.0 \text{ mg/ml}$ 的康柏西普 $0.05 \text{ ml}$ (含康柏西普 $0.5 \text{ mg}$ ),于角膜缘后 $3.75 \text{ mm}$ 处垂直进针,缓慢推注。注射完毕后,涂氧氟沙星眼膏,包眼。注射1次后,根据复诊情况决定是否重复治疗。若BCVA下降2行及以上或CMT增加 $\geq 100 \mu\text{m}$ ,则予以相同抗VEGF药物治疗。两次IVR时间至少间隔4周。

IVR后1周行激光光凝治疗。采用美国科医人公司多波长激光机,通过全视网膜激光镜,对FFA检查显示的无灌注区范围行象限性光凝。激光参数:光斑直径 $50 \sim 100 \mu\text{m}$ ,曝光时间 $0.2 \text{ s}$ ,光斑反应I~II级,光凝

斑间距约1个光斑直径。治疗后给予普拉洛芬眼液滴眼,4次/d,连续3 d。1次光凝范围 $\leq 1/4$ 个象限,2次光凝时间间隔1周。出血浓密遮蔽视网膜无法完成光凝者,出血吸收后择期补充光凝。

根据文献[13]分类标准,玻璃体腔注射抗VEGF药物联合激光光凝治疗后1个月CMT较治疗前降低 $\leq 25\%$ 为治疗无应答, $>25\%$ 为治疗应答,并据此分为无应答组、应答组,分别为15例15只眼、26例26只眼。无应答组、应答组患者年龄、性别构成比较,差异无统计学意义( $t = -0.298, -1.708, P = 0.096, 0.767$ );患眼平均logMAR BCVA、CMT比较,差异无统计学意义( $t = 2.056, -1.876, P = 0.460, 0.070$ ) (表1)。

治疗后随访6~11个月,平均随访时间8个月。治疗后1 d,1周,1、3、6个月采用与治疗前相同的检查设备和方法行BCVA、OCT检查。观察无应答组、应答组患眼治疗后1、6个月logMAR BCVA、CMT变化。将随访时间 $\geq 6$ 个月时的logMAR BCVA定义为远期视力<sup>[14]</sup>。观察患眼治疗后远期视力与治疗前1个月CMT降低值、ELM、椭圆体带的相关性,以及与药物和治疗方式相关的眼部和全身不良反应发生情况。

采用SPSS19.0统计软件行统计学分析。数据以均数 $\pm$ 标准差( $\bar{x} \pm s$ )表示。组间年龄、性别、治疗前logMAR BCVA、治疗前CMT、治疗后6个月logMAR BCVA、治疗后6个月CMT、注药次数比较采用两独立样本 $t$ 检验。Pearson相关性分析远期视力与年龄、治疗前logMAR BCVA、治疗前CMT、注药次数、治疗后1个月CMT降低值的相关性。多元回归分析远期视力与年龄、性别、治疗前logMAR BCVA、治疗前CMT、注药次数、治疗后1个月CMT降低值、椭圆体带完整性、ELM完整性的相关性。 $P < 0.05$ 为差异有统计学意义。

## 2 结果

治疗后1个月,患眼平均CMT为 $(281.12 \pm 128.41) \mu\text{m}$ ,较治疗前降低 $(231.48 \pm 177.99) \mu\text{m}$ ;ELM、椭圆体带平均完整性分别为 $0.56 \pm 0.50, 0.41 \pm 0.50$ ;平均注药次数为 $(1.76 \pm 1.20)$ 次。治疗后6个月,患眼平均logMAR BVCA为 $0.48 \pm 0.34$ 。

表1 无应答组、应答组患者基线资料比较

组别	眼数(只)	年龄(岁)	男/女	logMAR BCVA	CMT( $\mu\text{m}$ )
无应答组	15	$55.93 \pm 8.61$	11/4	$0.99 \pm 0.49$	$443.27 \pm 141.35$
应答组	26	$56.81 \pm 9.27$	12/14	$0.73 \pm 0.34$	$552.62 \pm 198.01$
$t$ 值	-	-0.298	-1.708	2.056	-1.876
$P$ 值	-	0.767	0.096	0.460	0.068

Pearson相关性分析结果显示, 远期视力与治疗前logMAR BCVA以及治疗后1个月CMT降低值、注药次数呈正相关 ( $P < 0.05$ ); 与年龄、治疗前CMT无相关 ( $P > 0.05$ ) (表2)。多元回归分析结果显示, 远期视力与治疗前logMAR BVCA、治疗后1个月CMT降低值、ELM完整性、注药次数相关 ( $P < 0.05$ ); 与年龄、性别、治疗前CMT、椭圆体带完整性无相关 ( $P > 0.05$ ) (表3)。

表2 远期视力影响因素相关性分析结果

影响因素	r值	P值
年龄	0.052	0.745
治疗前logMAR BCVA	0.545	0.000
治疗前CMT	-0.103	0.521
治疗后1个月CMT降低值	0.568	0.000
注药次数	0.471	0.002

表3 远期视力影响因素的多元回归分析结果

自变量	t值	P值
年龄	-0.246	0.807
性别	-0.027	0.979
治疗前logMAR BCVA	4.652	0.000
治疗前CMT	2.301	0.027
治疗后1个月CMT降低值	5.752	0.000
ELM完整性	-5.063	0.000
椭圆体带完整性	-1.613	0.115
注药次数	0.348	0.730

治疗后6个月, 无应答组、应答组患眼logMAR BCVA分别为 $0.86 \pm 0.23$ 、 $0.26 \pm 0.14$ ; 平均CMT分别为( $398.93 \pm 104.87$ )、( $255.15 \pm 55.18$ )  $\mu\text{m}$ ; 平均注药次数分别为( $2.53 \pm 1.46$ )、( $1.31 \pm 0.74$ )次。两组患眼平均logMAR BCVA、CMT、平均注药次数比较, 差异均有统计学意义 ( $t=10.293$ 、 $5.773$ 、 $3.589$ ,  $P=0.000$ 、 $0.000$ 、 $0.001$ )。

随访中及末次随访时, 所有患者均未出现高血压、眼内炎、玻璃体积血、视网膜撕裂、医源性白内障等眼部并发症, 以及全身不良反应发生。

### 3 讨论

BRVO继发ME是导致患者视力降低的主要原因。康柏西普为全人源化重组融合蛋白, 可阻断VEGF-A所有亚型、VEGF-B及胎盘生长因子, 减少血管渗漏, 抑制血管内皮细胞的增生和新生血管的形成, 达到治疗ME<sup>[15]</sup>。激光光凝机制是感光细胞和RPE细胞的破坏使

内层视网膜的含氧量相对增加, 引起小动脉血管收缩, 毛细血管网及静脉血管压力相对减小, 从而减少血管渗漏达到减轻ME的目的<sup>[16]</sup>。

本研究结果显示, 远期BCVA与年龄、性别、治疗前CMT不相关, 而与治疗前BCVA呈正相关。治疗前BCVA越好, 远期BCVA预后越好, 反之亦然, 结果与文献报道一致<sup>[17]</sup>。已有研究证实病程与患者视力恢复程度相关<sup>[6]</sup>, 故本研究仅纳入病程 $< 3$ 个月的患者。视网膜静脉阻塞(RVO)早期激光光凝治疗, 可以加速视网膜出血、ME吸收, 有效保护患者现有视力、促进远期视力提高<sup>[18]</sup>。抗VEGF药物治疗RVO并发ME效果明显, 不良反应较少, 但疗效维持时间较短。发病早期及时抗VEGF药物治疗对患者更有益<sup>[19]</sup>。在侧支循环建立之前, 应尽可能减少ME, 避免光感受器的不可逆损伤, 减少其他可能发生的继发损害, 尽可能保持黄斑区正常形态。

本研究结果显示, 两组患眼治疗后1、6个月平均CMT均较治疗前降低, 结果与文献报道一致<sup>[20, 21]</sup>。治疗后1个月CMT降低值与远期视力呈正相关, 即CMT降低越大, 对康柏西普和激光光凝治疗应答越好, 远期视力恢复越好且注药次数越少, 复发后再注射治疗, 仍可获得较好视力预后; 反之, CMT降低值越小, 对治疗的应答反应越弱, 远期视力恢复越差且注药次数越多。提示治疗后1个月CMT降低值对后续治疗及远期视力评估有一定指导意义。

已有研究表明, 单纯椭圆体带断裂可以自行修复, 而联合ELM受损后, 椭圆体带不能恢复, 说明ELM在对椭圆体带损伤修复中起重要作用<sup>[22]</sup>。本研究结果显示, 治疗后1个月椭圆体带完整性与远期视力无相关性; 而Inoue等<sup>[23]</sup>研究发现治疗后12个月仍有患眼椭圆体带修复, 视力恢复。其原因我们推测可能与本研究观察时间短以及观察时间点不同所致。

本组患眼BCVA提高程度不及CMT降低明显, 提示ME是影响视功能的主要而非唯一因素。ME消退同时并非一定能完全恢复正常视功能。ELM层完整性的恢复可能对视功能的恢复起到较大作用, 首次治疗后1个月CMT的变化值与ELM层结构完整性, 对视力预后的评估可起到一定的提示价值。

本研究为回顾性分析以及样本量小、随访时间短和评价标准等存在不足, 其研究结果有待多中心、大样本、长期随访的随机对照试验进一步验证。

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