

1.2.2 观察项目 在治疗前及治疗1个月、3个月、6个月后,患者取坐位,调整眼球至合理位置,对黄斑中心凹进行OCTA栅栏状扫描,检测黄斑中心凹无血管区(FAZ)参数、黄斑区中心凹1 mm直径范围全层微血管密度;应用mf-ERG(RETISCAN 3·15系统,德国罗兰公司)检测黄斑区P₁、N₁波环1、环4反应密度,评估黄斑区视网膜功能。应用《国际标准视力表》检测视力,标准检查距离5 m。并应用OCT和FFA检测黄斑中心凹的垂直厚度和荧光素渗漏状况。

1.3 统计学方法 所有数据均采用SPSS 19.0统计学软件进行统计分析。计量资料采用 $\bar{x} \pm s$ 表示,组间、组内比较采用配对t检验;计数资料描述为N(%),采用 χ^2 检验。检验水准: $\alpha=0.05$ 。

2 结果

2.1 两组患者治疗前后OCTA和视力结果比较

两组治疗前与治疗1个月、3个月、6个月后FAZ和黄斑区视网膜血管密度比较以及对照组治疗前视力与治疗后比较,差异均无统计学意义(均为 $P>0.05$);试验组治疗后3个月和6个月视力均高于治疗前与同期对照组,差异均有统计学意义(均为 $P<0.05$)(见表2)。

表3 两组患者治疗前后mfERG检查P₁、N₁反应密度结果比较

组别	眼数	时间	P ₁ 波/nV·deg ⁻²		N ₁ 波/nV·deg ⁻²	
			环1	环4	环1	环4
对照组	40	治疗前	44.11±3.08	21.65±1.32	15.06±0.97	5.12±0.13
		治疗后1个月	56.24±2.71 [△]	23.30±1.43 [△]	17.15±0.86 [△]	5.58±0.15 [△]
		治疗后3个月	62.39±2.85 ^{△▲}	24.48±1.59 ^{△▲}	18.23±0.91 ^{△▲}	5.74±0.12 [△]
		治疗后6个月	69.26±3.04 ^{△▲☆}	26.15±1.42 ^{△▲☆}	19.30±0.76 ^{△▲☆}	5.88±0.14 ^{△▲☆}
试验组	40	治疗前	43.96±3.19	21.30±1.31	14.93±1.06	5.10±0.11
		治疗后1个月	60.31±3.26 [△]	23.42±1.15 [△]	17.42±1.01 [△]	5.70±0.13 [△]
		治疗后3个月	65.47±3.41 ^{△▲☆}	25.06±1.29 ^{△▲☆}	19.18±1.13 ^{△▲☆}	5.87±0.13 ^{△▲☆}
		治疗后6个月	73.50±3.60 ^{△▲☆☆}	27.43±1.18 ^{△▲☆☆}	20.76±1.05 ^{△▲☆☆}	5.93±0.12 ^{△▲☆☆}

注:与治疗前比较,[△] $P<0.05$;与治疗1个月比较,[▲] $P<0.05$;与治疗3个月比较,[☆] $P<0.05$;与对照组比较,[★] $P<0.05$

2.3 两组患者治疗前后OCT和FFA结果比较

两组治疗后1个月、3个月、6个月各项指标结果均优于治疗前,两组治疗后6个月时各项指标结果均优于同组治疗后1个月、3个月,差异均有统计学意

表2 两组患者治疗前后OCTA和视力结果比较

组别	眼数	时间	FAZ/mm ²	黄斑区视网膜血管密度/%	视力
对照组	40	治疗前	383.72±21.89	31.84±1.35	0.14±0.06
		治疗后1个月	379.06±20.15	31.21±1.37	0.20±0.08
		治疗后3个月	376.29±19.08	29.46±1.26	0.21±0.07
		治疗后6个月	375.43±18.29	28.65±1.18	0.23±0.08
试验组	40	治疗前	384.26±22.07	32.07±1.42	0.12±0.08
		治疗后1个月	378.19±20.64	31.03±1.50	0.23±0.16
		治疗后3个月	375.50±19.37	29.47±1.32	0.35±0.17 ^{△★}
		治疗后6个月	372.39±17.02	28.28±1.13	0.42±0.20 ^{△★}

注:与治疗前比较,[△] $P<0.05$;与对照组比较,[★] $P<0.05$

2.2 两组患者治疗前后mf-ERG的P₁、N₁波反应密度结果比较

两组治疗后1个月、3个月、6个月P₁、N₁波反应密度结果均优于治疗前,差异均有统计学意义(均为 $P<0.05$)。两组内除治疗后3个月与治疗后1个月N₁波环4同组指标结果比较差异无统计学意义(均为 $P>0.05$)外,两组内治疗后1个月、3个月、6个月其他同组各项指标结果比较,差异均有统计学意义(均为 $P<0.05$)。试验组治疗后3个月、6个月各项指标均高于同期对照组,差异均有统计学意义(均为 $P<0.05$)(见表3)。

义(均为 $P<0.05$)。两组间治疗后1个月、3个月、6个月时比较,差异均无统计学意义(均为 $P>0.05$)(见表4)。

表4 两组患者治疗前后OCT和FFA检测结果比较

组别	眼数	时间	OCT 检测结果	FFA 检测结果/例			
			中心视网膜厚度/ μm	局部渗漏	弥漫渗漏	囊样渗漏	合计
对照组	40	治疗前	382.15 \pm 24.28	21	12	7	40
		治疗后 1 个月	331.06 \pm 20.15 Δ	13	6	2	21 Δ
		治疗后 3 个月	326.17 \pm 21.34 Δ	12	5	1	18 Δ
		治疗后 6 个月	280.46 \pm 18.27 $\Delta\blacktriangle\star$	7	4	0	11 $\Delta\blacktriangle\star$
试验组	40	治疗前	383.04 \pm 22.86	20	12	8	40
		治疗后 1 个月	327.46 \pm 21.48 Δ	11	8	2	21 Δ
		治疗后 3 个月	285.19 \pm 20.61 Δ	9	4	1	14 Δ
		治疗后 6 个月	277.41 \pm 18.34 $\Delta\blacktriangle\star$	4	3	0	7 $\Delta\blacktriangle\star$

注:与治疗前比较,[△] $P<0.05$;与治疗1个月比较,[▲] $P<0.05$;与治疗3个月比较,[☆] $P<0.05$

3 讨论

DME 是糖尿病引起的常见眼底疾病,可发生于糖尿病视网膜病变的任何阶段,是糖尿病患者视力损害、甚至致盲的主要原因之一。其病理改变主要是局部视网膜微血管瘤、视网膜内微血管异常及毛细血管扩张、渗漏。激光光凝术目前仍是治疗黄斑水肿的首选方法,其优点在于疗效肯定、费用低,但会对视网膜造成不可逆的损伤,并且只能稳定而无法提高视力;玻璃体内注药术是近些年来,尤其在抗 VEGF 药物推出以后,全球范围内逐渐成为了治疗 DME 的一线方法^[6]。

本次研究结果显示,两组患者治疗后随着时间延长,mf-ERG 指标呈现好转趋势,试验组患者视力显著提高。视网膜黄斑部因缺血缺氧常出现水肿,严重损害患者视功能,格栅光凝治疗能够直接封闭扩张的毛细血管,减少渗漏,降低毛细血管通透性和血管内压,增加视网膜与脉络膜的通透性,阻止或延缓微循环障碍,改善局部代谢和缺血组织缺氧状态,并能够促进渗出物吸收^[7]。VEGF 又称为血管渗漏因子,DME 患者 VEGF 病理性释放增加,较正常眼内含量显著升高,是 DME 发展的重要原因之一^[8]。低氧条件下,可促进多种眼部细胞 VEGF 的释放,通过一系列分子信号转导通路和级联反应,启动炎症反应,增加视网膜血管内皮细胞通透性,并诱导血管内皮细胞增殖,促进病理性新生血管形成。康柏西普眼用注射液是一种 VEGF 受体与人免疫球蛋白 Fc 段基因重组的融合蛋白,能够特异性结合血管内皮生长因子 VEGF,竞争性抑制 VEGF 与受体,降低 VEGF 水平,并避免其被激活,抑制或降低内皮细胞增殖和血管新生,消除且减轻黄斑水肿,并不会损伤视网膜^[9],但缺点是药物价格昂贵,持续时间短(一般为 1 个月),常需重复注射。两种方法联合治疗,可达到安全、高效、经济的目的^[10]。

本研究结果显示,两组患者治疗后 FAZ、黄斑区视网膜血管密度、OCT 和 FFA 结果比较,差异均无统计学意义。采用 OCTA 评估 FAZ 以及黄斑部中心凹周围 1 mm 直径范围微血管密度在治疗前后变化,结果发现各项指标并未发生明显变化。在黄斑水肿严重的患眼中,视网膜毛细血管可能会被水肿组织推向外侧。其结果是水肿减退会带来血管密度的提高,但这可能仅仅反映了分层错误的修正,而不是血流的改善^[11]。以往研究表明,FAZ 面积在 DR 患者中是视网膜缺血的预后指标^[12]。Gong 等^[13]研究表明,继发于 DR 或视网膜静脉阻塞的黄斑囊样水肿经抗 VEGF 治疗后,FAZ 进展性增大,而 Takase 等^[14]其他研究则未发现此类变化。本研究我们测量了 FAZ 面积,结果显示,FAZ 面积在注射后保持稳定。尽管水肿的囊腔可以通过影响毛细血管的位置来影响 FAZ 的边界,但我们并未发现 FAZ 和黄斑中

心凹周围血流密度发生显著变化,尚需进一步研究^[15]。

mf-ERG 是一种新生的视觉电生理检查技术,能够较敏感地检测视网膜许多细小部位的电反应,通过立体图直观地显示相应部位的振幅密度,并能在二维图上分析不同象限、不同环的振幅密度及潜伏期,定量地发现视功能局部变化的程度和范围,客观、准确地反映相应部位的功能状态。克服了全视野视网膜电图难以对局部病变进行检测的弊端,可对整个视野中细小部位的视网膜电图进行测量,对评估眼底局部细微的病变具有高敏感性^[16-17]。

综上所述,在黄斑格栅光凝基础上,联合康柏西普眼内注药治疗 DME 患者,能够显著改善患者黄斑、视网膜结构和功能,提高患者视力水平。

参考文献

[1] MEHMET T, ZAFER Y, SERDAR A, HACI M S, FATI H O. VEGF-A gene polymorphisms and responses to intravitreal ranibizumab treatment in patients with diabetic macular edema[J]. *Int Ophthalmol*, 2018, 38(6): 2381-2388.

[2] 卢谦益. 阿柏西普经玻璃体内注射治疗糖尿病黄斑水肿的临床疗效[J]. *眼科新进展*, 2019, 39(4): 340-342.

[2] LU Q Y. Intravitreal aflibercept injection for the treatment of diabetic macular edema[J]. *Rec Adv Ophthalmol*, 2019, 39(4): 340-342.

[3] 黄超, 赵永, 王梅, 喻亚梅. OCT 血管成像术在中心性渗出性脉络膜视网膜病变中的应用[J]. *临床眼科杂志*, 2019, 27(2): 118-121.

[3] HUANG C, ZHAO Y, WANG M, YU Y M. Application of OCT angiography in central exudative chorioretinopathy[J]. *J Clin Ophthalmol*, 2019, 27(2): 118-121.

[4] 李玲, 陈婷妍, 梁勇. 糖尿病性黄斑水肿的早期诊断与治疗[J]. *国际眼科杂志*, 2014, 14(10): 1809-1811.

[4] JI L, CHEN T Y, LIANG Y. Early diagnosis and treatment of diabetic macular edema[J]. *Int Eye Sci*, 2014, 14(10): 1809-1811.

[5] 张召弟, 郭晨, 帅天姣, 朴天华. 玻璃体内注射康柏西普对弥漫性糖尿病性黄斑水肿的影响[J]. *眼科新进展*, 2018, 38(1): 69-72.

[5] ZHANG Z D, GUO S, SHUAI T J, PIAO T H. Effect of intravitreal injection of conbercept on diabetic diffuse macular edema[J]. *Rec Adv Ophthalmol*, 2018, 38(1): 69-72.

[6] 田秀红. 黄斑区格栅样光凝与玻璃体腔注射雷珠单抗治疗糖尿病黄斑水肿的疗效观察[J]. *中国处方药*, 2017, 15(7): 76-77.

[6] TIAN X H. Effect of grille-like photocoagulation in macular area and intravitreal injection of Leizhu McAb on diabetic macular edema[J]. *J China Prescr Drug*, 2017, 15(7): 76-77.

[7] NIMET Y E, SERHAT I, ESRA T K, NURSAL M Y, HANDAN B, YAVUZ B. Influence of serous retinal detachment on the outcome of ranibizumab treatment in diabetic macular oedema[J]. *Cutan Ocul Toxicol*, 2018, 37(4): 324-327.

[8] 刘彦, 陈建华, 赵慧英, 吴香丽, 殷英霞, 陈冬军. 康柏西普玻璃体腔注射联合激光光凝对糖尿病黄斑水肿患者脉络膜厚度的影响[J]. *陕西医学杂志*, 2019, 48(8): 1063-1066.

[8] LIU Y, CHEN J H, ZHAO H Y, WU X L, YIN Y X, CHEN D J. Clinical observation of intravitreal injection of Conbercept combined with laser photocoagulation for diabetic macular edema[J]. *Shaanxi Med J*, 2019, 48(8): 1063-1066.

[9] 陈震, 许阿敏, 夏沁韵. 玻璃体内注射阿柏西普治疗糖尿病黄斑水肿的疗效[J]. *武汉大学学报(医学版)*, 2019, 40(5): 842-844.

[9] CHEN Z, XU A M, XIA Q Y. Intravitreal injection of Aflibercept for the treatment of diabetic macular edema[J]. *Med J Wuhan Univ*, 2019, 40(5): 842-844.

[10] 宋爱萍, 于涛, 卓建, 曲鹏. 近视患者黄斑区视网膜多焦视网膜电图和光学相干断层扫描的评估和分析[J]. *眼科新进展*, 2019, 39(3): 255-259.

- SONG A P, YU T, ZHUO J, QU P. Evaluation and analysis of macular retina by multifocal electroretinogram and optical coherence tomography in myopia[J]. *Rec Adv Ophthalmol*, 2019, 39(3):255-259.
- [11] 孙沅, 王健, 孙沂, 张晓梅, 魏海英, 葛亮. OCTA 用于检测不同屈光人群的黄斑区视网膜密度和厚度及其相关性分析[J]. 现代生物医学进展, 2019, 19(14):2797-2800.
- SUN Y, WANG J, SUN Y, ZHANG X M, WEI H Y, GE L. Detection and Correlative Analysis of the Retinal Density and Thickness in the Macular Area in Patients with Different Refractive Light[J]. *Prog Mod Biomed*, 2019, 19(14):2797-2800.
- [12] BALARATNASINGAM C, MAIKO I, SEUNGJUN A, JESSE M, ELONA D G, LAWRENCE A Y, et al. Visual acuity is correlated with the area of the foveal avascular zone in diabetic retinopathy and retinal vein occlusion[J]. *Ophthalmology*, 2016, 123(11):2352-2367.
- [13] GONG D, YU W H, ZHANG X, YANG Z K, ZOU X, QU Y, et al. A morphological study of the foveal avascular zone in patients with diabetes mellitus using optical coherence tomography angiography[J]. *Graefes Arch Clin Exp Ophthalmol*, 2016, 254(5):873-879.
- [14] TAKASE N, NOZAKI M, KATO A, OZEKI H, YOSHIDA M, OGURA Y. Enlargement of foveal avascular zone in diabetic eyes evaluated by en face optical coherence tomography angiography[J]. *Retina*, 2015, 35(11):2377-2383.
- [15] LITTLEWOOD, MOLLAN, PAPPER, HICKMAN. The utility of fundus fluorescein angiography in neuro-ophthalmology[J]. *Neuroophthalmology*, 2019, 43(4):217-234.
- [16] 刘景祥, 姜玉莹, 陈丽丽, 李林. FFA 联合黄斑 OCT 在糖尿病性视网膜病变诊断及评价疗效中的应用[J]. 中国实验诊断学, 2016, 20(8):1287-1288.
- LIU J X, JIANG Y Y, CHEN L L, LI L. FFA combined with macular OCT in diagnosis and evaluation of diabetic retinopathy[J]. *Chin J Lab Diagn*, 2016, 20(8):1287-1288.
- [17] 齐佳, 郭蕊, 周云, 代琴. 应用多焦视网膜电图进行激光治疗糖尿病视网膜病变的临床研究[J]. 临床眼科杂志, 2017, 25(2):125-128.
- QI J, GUO R, ZHOU Y, DAI Q. The clinical study of laser treatment of diabetic retinopathy with multi focus[J]. *J Clin Ophthalmol*, 2017, 25(2):125-128.

The effect of conbercept combined with macular grid photocoagulation on diabetic macular edema

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[Abstract] Objective To evaluate the efficacy of macular grid photocoagulation, combined with conbercept intraocular injection for patients with diabetic macular edema (DME) by optical coherent tomography angiography (OCTA) and multifocal electroretinogram (mf-ERG), and to analyze the mechanism of treatment. **Methods** Totally 80 DME patients in hospital from April in 2017 to July in 2018 were enrolled, and they were randomly divided into control group and experimental group, 40 patients in each group. Control group was treated with macular grid photocoagulation, and the experimental group was given conbercept combined with macular grid photocoagulation. OCTA and mf-ERG were used to detect macular and retinal function and visual status before treatment and at 1 month, 3 months, and 6 months after treatment. Macular foveal thickness and fluorescein leakage were detected by optical coherence tomography (OCT) and fluorescein fundus angiography (FFA). **Results** There were no significant differences in foveal avascular zone (FAZ) and macular retinal vascular density between before treatment and 1 month, 3 months, and 6 months after treatment in the both groups, as well as in visual acuity of the control group pre-treatment and post-treatment (all $P > 0.05$). The visual acuity of the experimental group was higher than that of the control group at 3 months and 6 months after treatment and before surgery ($P < 0.05$). The response density of P_1 and N_1 rings 1 and 4 of mf-ERGs in the experimental group at 3 months, and 6 months after treatment were higher than those in the control group, and the differences were statistically significant (both $P < 0.05$). In the both groups, the results of OCT and FFA 1 month, 3 months, and 6 months after treatment were better than those of before treatment, the results of which after treatment 6 months were better than 1 month and 3 months after treatment, and the differences were statistically significant (all $P < 0.05$). There was no significant difference in OCT and FFA after treatment between the two groups (all $P > 0.05$). **Conclusion** Macular grid photocoagulation combined with conbercept intraocular injection for the treatment of DME patients can significantly improve the patient's macular, retinal structure and function, and visual acuity.

[Key words] diabetic macular edema; conbercept; grid photocoagulation; optical coherent tomography angiography; multifocal electroretinogram