·临床报告·

抗 VEGF 联合激光治疗重度非增殖期糖尿病视网膜病变对黄斑区血流密度的影响

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摘要

目的:探讨抗血管内皮生长因子(VEGF)联合全视网膜光凝术(PRP)治疗重度非增殖期糖尿病视网膜病变(sNPDR)合并黄斑水肿(DME)对黄斑区血流密度变化的影响。

方法:回顾性选取 2018-10/2019-04 在我院确诊的 sNPDR 合并 DME 患者 30 例 30 眼,根据治疗方案进行分组,其中 A 组 15 例 15 眼采用"1+PRN"方案采用玻璃体腔内注射雷珠单抗 7d 后行 PRP 治疗,B 组 15 例 15 眼采用单纯 PRP 治疗。对比两组治疗前后黄斑区 6mm×6mm 浅层毛细血管(SCP)和深层毛细血管(DCP)血流密度、黄斑中心凹厚度(CMT)、最佳矫正视力(BCVA)变化情况。

结果:与术前相比,A 组患者术后 2wk,1mo DCP 血流密度显著增加、CMT 明显降低、BCVA 明显改善(均 $P<0.05$),B 组患者术后 1mo CMT 降低、BCVA 改善(均 $P<0.05$)。术后 2wk、1mo,A 组患者 DCP 血流密度较 B 组明显增加(43.37%±2.72% *vs* 41.03%±2.60%,45.01%±2.28% *vs* 41.20%±2.43%,均 $P<0.05$),CMT 较 B 组明显降低(303.4±30.36μm *vs* 329.60±31.47μm,268.67±30.27μm *vs* 319.40±28.63μm,均 $P<0.05$),BCVA(LogMAR)较 B 组明显改善(0.28±0.11 *vs* 0.40±0.13,0.23±0.14 *vs* 0.38±0.15,均 $P<0.05$)。

结论:抗 VEGF 联合 PRP 治疗 sNPDR 合并 DME 患者短期内可有效增加 DCP 血流密度,减轻黄斑水肿,改善视力。

关键词:黄斑血流密度;重度非增殖期糖尿病视网膜病变;黄斑水肿;抗血管内皮生长因子;全视网膜光凝术
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Effect of anti-VEGF combined with laser therapy on macular blood flow density in patients with severe non-proliferative diabetic retinopathy

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Abstract

• AIM: To investigate the effect of anti-VEGF combined with panretinal photocoagulation (PRP) in the treatment of severe non-proliferative diabetic retinopathy (sNPDR) with diabetic macular edema (DME) on the change of macular blood flow density.

• METHODS: Data of 30 eyes in 30 patients at Guangxi Zhuang Autonomous Region People's Hospital from October 2018 to April 2019 were retrospectively reviewed, and they were randomly divided into group A and group B each with 15 cases. Group A was received PRP treatment after one initial intravitreal ranibizumab injection followed by pro re nata (PRN) at 7d, while group B was administered PRP alone. The blood flow density of superficial capillary plexus (SCP) and deep capillary plexus (DCP) in macular area (6mm × 6mm), central macular thickness (CMT), and best corrected visual acuity [BCVA (LogMAR)] were compared between the two groups before and after treatment.

• RESULTS: Compared with before operation, the DCP blood flow density was significantly increased, CMT was obviously decreased, and BCVA was markedly improved in group A at 2wk and 1mo after surgery (all $P<0.05$),

while CMT was decreased and BCVA was improved in group B at 1mo after operation (all $P<0.05$). Postoperative in group A at 2wk and 1mo, the DCP blood flow density was significantly higher than that in group B (43.37%±2.72% *vs* 41.03%±2.60%, 45.01%±2.28% *vs* 41.20%±2.43%, $P<0.05$), CMT was obviously lower than group B (303.4±30.36μm *vs* 329.60±31.47μm, 268.67±30.27μm *vs* 319.40±28.63μm, all $P<0.05$), and BCVA (LogMAR) was markedly improved compared with group B (0.28±0.11 *vs* 0.40±0.13, 0.23±0.14 *vs* 0.38±0.15, all $P<0.05$).

• CONCLUSION: Anti-VEGF combined with PRP can effectively increase DCP blood flow density, reduce macular edema and improve visual acuity in the short term in patients with sNPDR with DME.

• KEYWORDS: macular flow density; severe non-proliferative diabetic retinopathy; macular edema; anti-VEGF; panretinal photocoagulation

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0 引言

糖尿病视网膜病变(diabetic retinopathy, DR)是常见的、重要的致盲性眼部病变[1],而DR合并糖尿病黄斑水肿(diabetic macular edema, DME)是致盲的重要原因[2]。研究发现,血管内皮生长因子(vascular endothelial growth factor, VEGF)能增加视网膜血管通透性,是导致DME的关键,同时VEGF又是DR发展的重要原因[3-5]。近年研究发现,抗VEGF药物对DME疗效显著[6],是治疗DR的重要手段[7-8]。而抗VEGF药物联合全视网膜光凝术(panretinal photocoagulation, PRP)是重度非增殖期糖尿病视网膜病变(severe non-proliferative diabetic retinopathy, sNPDR)合并DME的有效治疗手段[9]。DR患者视网膜微循环缺血,且DR的严重程度与视网膜血流密度相关[10]。目前抗VEGF药物对视网膜微循环的影响尚未明确。有研究发现抗VEGF药物可使视网膜微循环发生缺血[11],但有研究认为其很少进一步损害视网膜微循环[12],且短期内不影响视网膜血流[13],甚至有研究发现其能增加视网膜血流[14]。因此,抗VEGF药物在减轻DME同时是否使视网膜缺血加重,而抗VEGF药物联合PRP治疗sNPDR对黄斑区视网膜血流的影响又如何,值得探讨。

光学相干断层扫描血管造影(optical coherence tomography angiography, OCTA)技术可快速、无创地对视网膜微血管可视化,并能量化血流密度[15-17]。本研究拟利用OCTA观察sNPDR合并DME患者行抗VEGF联合PRP治疗及单纯PRP治疗后黄斑区浅层毛细血管丛(superficial capillary plexus, SCP)、深层毛细血管丛(deep capillary plexus, DCP)血流密度及黄斑中心凹厚度(central macular thickness, CMT)和最佳矫正视力(best corrected visual acuity, BCVA)的变化。

1 对象和方法

1.1 对象 回顾性病例对照研究。选取2018-10/2019-04就诊于广西壮族自治区人民医院并确诊为sNPDR合并DME的患者30例30眼,根据治疗方案进行分组,A组患者15例15眼,其中男8例,女7例,于玻璃体腔注射0.5mg雷珠单抗7d后予PRP治疗;B组患者15例15眼,其中男10例,女5例,行单纯PRP治疗。本研究获得广西壮族自治区人民医院伦理委员会审批,患者均对治疗方案知情同意并签署知情同意书。

1.1.1 纳入标准 (1)临床诊断均符合2014年中国DR诊疗指南[18],符合国际sNPDR诊断标准;(2)均行眼底照相及眼底荧光血管造影(fundus fluorescein angiography, FFA)检查,经主任医师判读结果,确诊为sNPDR合并DME,水肿累及黄斑中心;(3)经OCT检查,CMT 250~400μm,符合激光治疗和抗VEGF指征;(4)患眼BCVA<1.0(LogMAR),屈光不正≤±4D;(5)Goldman压平式眼压(intraocular pressure, IOP)<21mmHg;(6)随机血糖≤11.1mmol/L,血压≤150/90mmHg;(7)坚持随访者,随访期间血糖及血压控制在上述范围;(8)OCTA影像扫描质量值≥4。

1.1.2 排除标准 (1)合并眼前节炎症、青光眼、外伤等疾病;(2)合并其他黄斑部疾病或其他视网膜病变;(3)有眼底激光或手术史;(4)有严重影响影像学检查质量的眼病;(5)合并严重心脑肝肾疾病者;(6)近期全身或局部使用免疫抑制剂、激素等药物;(7)对本研究使用药物过敏者。

1.2 方法

1.2.1 治疗方法

1.2.1.1 抗VEGF治疗 A组患者采用"1+PRN"治疗方案。患者仰卧位,表面麻醉(盐酸丙美卡因),碘伏消毒皮肤,铺巾,用1mL无菌注射器针头在距离角膜缘约4.0mm处睫状体扁平部垂直巩膜面进针,玻璃体腔注入0.5mg雷珠单抗后予氧氟沙星眼膏包眼。

1.2.1.2 PRP治疗 散瞳及表面麻醉后采用眼科激光光凝机行PRP治疗。设置参数:光斑直径200μm,曝光时间0.05s,功率110~300mW,光斑数目1200~2000点。光凝范围:距视盘上下及鼻侧缘1PD,黄斑颞侧2PD以外至赤道部,采用点扫描距阵激光模式,光斑强度Ⅱ~Ⅲ级。患者均一次性完成PRP,中途可予休息1~2min。两组患者激光用法、参数及疗程一致。

1.2.2 观察指标 治疗前后两组患者均行BCVA、IOP、眼底照相[19]、随机血糖及血压等检查,并行OCTA检查。BCVA检查采用5m国际标准对数视力表检查,结果换算成LogMAR视力进行统计分析。OCTA检查利用RTVue-XR Avanti OCTA系统选择HD Angio-retina 6mm×6mm扫描模式,以患眼黄斑中心凹进行扫描,根据机器自带的AngioVue软件对患眼黄斑区的SCP、DCP血流密度进行检测,同时检测CMT,选择图像质量评分≥4者,记录数值。

统计学分析:应用SPSS 25.0软件对所研究数据进行统计学分析。计量资料以 $\bar{x}\pm s$ 表示,两组间比较采用独立样本 t 检验,两组治疗前后各时间点比较用双因素重复测量方差分析,进一步组内各时间点两两比较用LSD-t检验。计数资料用频数(n)表示,两组间比较采用Fisher确切概率法。$P<0.05$表示差异有统计学意义。

2 结果

2.1 两组患者基本资料比较 两组患者年龄、糖尿病(diabetes mellitus, DM)病程、随机血糖、收缩压、舒张压、眼压进行比较,差异均无统计学意义($P>0.05$,表1)。

表 1 两组患者基本资料比较

组别	例数	男/女(例)	年龄($\bar{x}\pm s$,岁)	DM 病程($\bar{x}\pm s$,mo)	随机血糖($\bar{x}\pm s$,mmol/L)	收缩压($\bar{x}\pm s$,mmHg)	舒张压($\bar{x}\pm s$,mmHg)	IOP($\bar{x}\pm s$,mmHg)
A 组	15	8/7	51.80±7.05	48.73±25.01	7.65±1.09	130.73±6.57	77.67±6.07	13.61±2.39
B 组	15	10/5	52.67±6.50	44.27±23.96	7.13±1.08	129.73±6.32	78.53±6.99	14.31±2.21
t		-	0.350	0.499	1.308	0.425	0.363	0.826
P		0.710	0.729	0.621	0.202	0.674	0.720	0.416

注:A 组:采用玻璃体腔注射雷珠单抗联合 PRP 治疗;B 组:采用单纯 PRP 治疗。-表示采用 Fisher 确切概率法。

表 2 两组患者治疗前后 SCP 和 DCP 血流密度比较 ($\bar{x}\pm s$,%)

组别	SCP			DCP		
	术前	术后 2wk	术后 1mo	术前	术后 2wk	术后 1mo
A 组	38.01±2.59	37.52±3.08	38.50±2.72	40.79±2.19	43.37±2.72[a]	45.01±2.28[a,c]
B 组	37.49±2.18	38.02±2.74	38.43±2.93	40.13±1.52	41.03±2.60	41.20±2.43
t	0.602	0.469	0.071	0.958	2.417	4.434
P	0.552	0.643	0.944	0.346	0.022	<0.001

注:A 组:采用玻璃体腔注射雷珠单抗联合 PRP 治疗;B 组:采用单纯 PRP 治疗。[a]P<0.05 *vs* 同组术前;[c]P<0.05 *vs* 术后 2wk。

表 3 两组治疗前后 CMT 和 BCVA 比较 $\bar{x}\pm s$

组别	CMT(μm)			BCVA(LogMAR)		
	术前	术后 2wk	术后 1mo	术前	术后 2wk	术后 1mo
A 组	335.53±32.43	303.4±30.36[a]	268.67±30.27[a,c]	0.40±0.13	0.28±0.11[a]	0.23±0.14[a,c]
B 组	332.07±31.80	329.60±31.47	319.40±28.63[a,c]	0.42±0.11	0.40±0.13	0.38±0.15[a]
t	0.295	2.320	4.716	0.445	2.727	2.774
P	0.770	0.028	<0.001	0.652	0.011	0.010

注:A 组:采用玻璃体腔注射雷珠单抗联合 PRP 治疗;B 组:采用单纯 PRP 治疗。[a]P<0.05 *vs* 同组术前;[c]P<0.05 *vs* 术后 2wk。

2.2 两组患者治疗前后 SCP 和 DCP 血流密度比较 治疗前后,两组患者 SCP 血流密度比较差异无统计学意义($F_{组间}=0.002$, $P_{组间}=0.969$; $F_{时间}=1.538$, $P_{时间}=0.224$; $F_{组间\times时间}=0.617$, $P_{组间\times时间}=0.543$),但两组患者 DCP 血流密度比较差异有统计学意义($F_{组间}=10.191$, $P_{组间}=0.003$; $F_{时间}=22.844$, $P_{时间}<0.001$; $F_{组间\times时间}=7.839$, $P_{组间\times时间}=0.001$),见表 2。A 组患者 DCP 血流密度治疗前后两两相比,术后 2wk,1mo 均较术前明显增加,且术 1mo 较术后 2wk 明显增加,差异有统计学意义($t=4.773$, $P<0.001$; $t=7.813$, $P<0.001$; $t=2.711$, $P=0.011$);B 组患者 DCP 血流密度治疗前后两两相比,差异无统计学意义($t=1.661$, $P=0.108$; $t=1.983$, $P=0.057$; $t=0.286$, $P=0.777$)。术前两组患者 DCP 血流密度差异无统计学意义($P>0.05$),术后 2wk,1mo A 组患者 DCP 血流密度较 B 组显著增加,差异均有统计学意义($P<0.05$)。

2.3 两组患者治疗前后 CMT 和 BCVA 比较 治疗前后,两组患者 CMT 比较差异有统计学意义($F_{组间}=4.982$, $P_{组间}=0.034$; $F_{时间}=162.328$, $P_{时间}<0.001$; $F_{组间\times时间}=75.189$, $P_{组间\times时间}<0.001$),见表 3。A 组患者 CMT 治疗前后两两相比,术后 2wk,1mo 较术前及术后 1mo 较术后 2wk 均明显降低,差异有统计学意义($t=11.621$, $P<0.001$; $t=22.767$, $P<0.001$; $t=9.589$, $P<0.001$);B 组患者 CMT 治疗前后两两相比,术后 2wk 与术前差异无统计学意义($t=0.892$, $P=0.380$),术后 1mo 较术前及术后 2wk 均明显降低,差异有统计学意义($t=4.313$, $P<0.001$; $t=2.816$, $P=0.009$)。术前两组患者 CMT 差异无统计学意义($P>0.05$),术后 2wk,1mo A 组患者 CMT 较 B 组明显降低,差异均有统计学意义($P<0.05$)。

治疗前后,两组患者 BCVA 比较差异有统计学意义($F_{组间}=4.569$, $P_{组间}=0.041$; $F_{时间}=31.957$, $P_{时间}<0.001$; $F_{组间\times时间}=12.809$, $P_{组间\times时间}<0.001$),见表 3。A 组患者 BCVA 治疗前后两两相比,术后 2wk,1mo 较术前及术后 1mo 较术后 2wk 均明显改善,差异有统计学意义($t=6.00$, $P<0.001$; $t=10.44$, $P<0.001$; $t=2.35$, $P=0.024$);B 组患者 BCVA 治疗前后两两相比,术后 1mo 与术前差异有统计学意义($t=2.50$, $P=0.019$)。术前两组患者 BCVA 差异无统计学意义($P>0.05$),术后 2wk,1mo A 组患者 BCVA 较 B 组明显改善,差异均有统计学意义($P<0.05$)。

3 讨论

据国际糖尿病联盟研究指出,2019 年全世界范围内已有近十亿人患有 DM,并预计在 2030 年和 2045 年分别增加 25%、51%[20]。在我国 DM 患者的人数亦随着生活条件改善而日渐增多,同时 DR 的发病率也不断攀升。DR 分为非增殖期糖尿病视网膜病变(non-proliferative diabetic retinopathy, NPDR)和增殖期糖尿病视网膜病变(proliferative diabetic retinopathy, PDR)[21]。sNPDR 如得不到及时、正确的干预,极易进展成 PDR,对患者视力造成极大程度的威胁。因此,积极正确的治疗对延缓及控制 sNPDR 的进展至关重要。

PRP 是 DR 的有效治疗手段[22-23]。PRP 能将 2a 内严重视力丧失的风险降低 60%,尤其是 PDR[23]。PRP 使视网膜色素上皮(retinal pigment epithelium, RPE)层吸收光能后由瘢痕组织取代,通过降低外层视网膜氧耗,减轻内层视网膜缺氧,同时能抑制 VEGF 产生并促进其消退,进

而改善DR患者的视网膜功能[22]。但是,单纯激光治疗不能修复已有的视功能损害,部分患者会出现黄斑水肿加重视功能损伤[21]。

VEGF不仅是血管生成的诱导剂,而且是血管渗漏的增强剂[24]。VEGF既能促进血管内皮细胞增殖,诱导血管生成,还能破坏内皮间的紧密连接,导致视网膜微循环屏障的破裂及组织渗漏[25-26]。2018年国际眼科委员会提出抗VEGF药物是治疗sNPDR的重要手段[27]。抗VEGF药物可通过调控血-视网膜屏障功能的途径减少黄斑区血管渗漏,进而减轻DME[28]。对于合并DME的DR患者,抗VEGF联合PRP治疗可使其获得更佳的视力,并可减少注射抗VEGF药物的次数[29],获得更高的成本效益[30]。

DR患者的黄斑区视网膜微循环普遍缺血,SCP、DCP血流密度低于正常人[31]。许多研究表明,在NPDR患者中,浅、深层血流密度均明显降低[32-35]。DR的血管病变主要发生在视网膜深层,黄斑中心凹周围DCP的完整性与DME发生相关[36]。NPDR的DCP血流密度比SCP血流密度影响更为严重,从轻度-中度-重度NPDR中DCP血流密度逐渐减少[37]。此外,DCP血流密度较SCP和脉络膜毛细血管血流密度具有更好的识别DR严重程度的能力[38]。本研究结果显示,抗VEGF联合PRP治疗sNPDR合并DME能明显改善DCP血流密度,但对SCP血流密度无明显影响,与单纯DME患者经抗VEGF治疗后DCP血流密度改善的研究结果相似[39]。李可嘉等[40]在视网膜分支静脉阻塞伴黄斑水肿的研究中亦发现抗VEGF药物治疗对SCP血流密度无影响,而DCP血流密度明显增加。本研究中,单纯PRP治疗sNPDR时黄斑区SCP、DCP血流密度均未见明显改变。Faghihi等[41]研究亦发现sNPDR患者在单纯PRP术后1mo,黄斑中心凹和中心凹区域的SCP和DCP血流密度没有显著变化。因此,本研究结果表明,注射抗VEGF药物后能改善sNPDR患者深层视网膜血液循环。此外,本研究中抗VEGF联合PRP组在DCP血流密度增加时,CMT减轻,视力亦得到改善,而单纯PRP组在术后1mo CMT和BCVA虽有改善,但抗VEGF联合PRP组的改善程度较为显著。其可能的原因为黄斑水肿多位于视网膜深层,VEGF通过破坏DCP屏障使其通透性及渗漏增加,促进DME发生,而水肿又进一步压迫DCP,使其血流减少,当注射抗VEGF药物后,毛细血管通透性降低,促进水肿吸收,DCP血流密度亦得到改善,从而改善视力。

综上所述,抗VEGF联合PRP治疗sNPDR合并DME在短期内能明显改善DCP血流密度,并能明显减轻黄斑水肿,改善患者的视力,对减缓及控制DR患者的病情具有较高的应用价值。同时,OCTA可动态监测并量化视网膜毛细血管丛的血流密度,监测视网膜形态和功能改变,能为DR患者抗VEGF的持续治疗提供客观的评价指标。但本研究病例纳入量较少,而且OCTA对于CMT值较大的DME患者自动分层系统可能存在偏差,因此下一步我们将增加样本量做进一步的验证。

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