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视网膜光凝术联合雷珠单抗治疗新生血管青光眼的疗效 及对血液流变学和房水炎症因子的影响*

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摘要 目的:探讨新生血管青光眼采用视网膜光凝术联合雷珠单抗治疗的疗效及对房水炎症因子和血液流变学的影响。**方法:**选取我院 2015 年 2 月~2017 年 5 月收治的 172 例(180 眼)新生血管青光眼患者作为研究对象,按照随机数字表法分为两组,对照组患者 85 例(88 眼),采用视网膜光凝术进行治疗,观察组患者 87 例(92 眼),采用视网膜光凝术联合雷珠单抗进行治疗,对比两组治疗后虹膜新生血管消退情况及消退时间,治疗前后眼压变化情况和静脉循环时间、眼部光学相干断层扫描(OCT)、血液流变学、房水炎症因子检测结果与不良反应发生情况。**结果:**观察组虹膜新生血管消失率为 95.65%,高于对照组的 80.68%($P<0.05$);与对照组对比,观察组虹膜新生血管消退时间更短($P<0.05$);与对照组对比,观察组治疗后眼压更低,静脉循环时间更短($P<0.05$);与对照组对比,观察组治疗后视野缺损值更小,视网膜神经纤维层(RNFL)厚度更厚($P<0.05$);治疗后观察组血浆黏度(PV)、红细胞压积(HCT)、血小板黏附率(PAdT)水平均低于对照组($P<0.05$);治疗后观察组房水炎症因子水平包括白介素-1 β (IL-1 β)、白介素-6(IL-6)、单核细胞趋化蛋白 1(MCP-1)水平均低于对照组($P<0.05$);对照组不良反应发生率为 9.09%,与对照组的 10.87%对比无统计学差异($P>0.05$)。**结论:**新生血管青光眼采用视网膜光凝术联合雷珠单抗治疗的疗效理想,可改善患者的血液流变学指标,降低房水炎症因子水平,且安全性高。

关键词:新生血管青光眼;视网膜光凝术;雷珠单抗;疗效;血液流变学;炎症因子

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Effect of Retinal Photocoagulation Combined with Leizumab in the Treatment of Neovascular Glaucoma and Its Effect on Hemorheology and Inflammatory Factors of Atrial Fluid*

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ABSTRACT Objective: To investigate the effect of retinal photocoagulation combined with leizumab in the treatment of neovascular glaucoma and its effect on hemorheology and inflammatory factors of atrial fluid. **Methods:** From February 2015 to May 2017, 172 cases (180 eyes) of neovascularization glaucoma patients were treated in our hospital were selected as the research object. According to random number table method, they were divided into two groups, control group patients with 85 cases (88 eyes), they were used the retinal photocoagulation treatment, observation group of patients with 87 cases (92 eyes), they were used the retinal photocoagulation combined with licensed resistance treatment. After treatment, iris neovascularization regression and regression time, intraocular pressure changes and venous circulation time before and after treatment, eye optical coherence tomography (OCT), hemorheology, aqueous humor inflammatory factors detection results and adverse reactions were compared between the two groups. **Results:** The rate of iris neovascularization status was 95.65% in the observation group, which was higher than 80.68% in the control group ($P<0.05$). Compared with the control group, the iris neovascularization regression time in the observation group was shorter($P<0.05$). Compared with the control group, the intraocular pressure in the observation group was lower after treatment, the venous circulation time was shorter after treatment ($P<0.05$). Compared with the control group, the visual field defect value in the observation group after treatment was smaller and the Retinal nerve fiber layer (RNFL) thickness was thicker ($P<0.05$). After treatment, the levels of plasma viscosity (PV), hematocrit (HCT) and platelet adhesion rate (PAdT) in the observation group were lower than those in the control group ($P<0.05$); the levels of inflammatory factors in aqueous humor including IL-1 β , IL-6 and MCP-1 in the observation group were lower than those in the control group ($P<0.05$); The incidence of adverse reactions in the observation group was 10.87%, with no significant difference compared with 9.09% in the control group ($P>0.05$). **Conclusion:** Retinal photocoagulation combined with ranibizumab is effective in the treatment of neovascular glaucoma. It can improve the hemorheological indexes, reduce the level of inflammatory factors of atrial fluid, and has high safety.

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前言

新生血管青光眼属于临床上一种常见的眼科疾病,是指患眼虹膜上有新生血管存在,主要表现为畏光、眼痛^[1,2]。患眼眼压可超过 60 mmHg,处于中度到重度充血状态,且通常会有角膜水肿伴随出现。以往临床通常会采用小梁切除术等手术方式对新生血管青光眼患者进行治疗,但治疗效果不佳,术后滤过泡区会有不同程度的纤维组织增生,使得滤过通道受阻,手术效果十分不理想^[3,4]。视网膜光凝术是现阶段临床治疗新生血管青光眼的常见方式之一,虽然能在一定程度上改善患者视力、眼压,但效果依然还有待进一步提高^[5,6]。雷珠单抗可对血管生成进行抑制,其属于单克隆抗体片段,通过与血管内皮生长因子相结合发挥作用^[7,8]。本研究在视网膜光凝术基础上联合雷珠单抗进行治疗,旨在为该疾病的治疗寻求更好的治疗办法,现报道如下。

1 资料与方法

1.1 资料来源

选取 2015 年 2 月~2017 年 5 月在我院接受治疗的 172 例(180 眼)新生血管青光眼患者作为研究对象,符合《同仁眼科手册·第 2 版》^[9]中新生血管青光眼的相关标准。纳入标准:①患者知情同意;②经常规眼科检查确诊;③患者对本次研究所用药物无禁忌症;④患者无精神疾病或意识障碍。排除标准:①中途退出;②存在全身严重性疾病;③存在眼部手术及外伤史;④视网膜脱离,屈光介质不清;⑤存在原发性青光眼病史。按照随机数字表法将患者分为两组,观察组患者共 87 例(92 眼),男性 51 例,女性 36 例;年龄 35-70 岁,平均(61.25±2.28)岁;糖尿病视网膜病变、其他类型病变分别有 43 眼、49 眼。对照组共 85 例(88 眼),男性 52 例,女性 33 例,年龄 33-71 岁,平均(61.98±2.23)岁;糖尿病视网膜病变、其他类型病变分别有 41 眼、47 眼。对比两组基础资料差异无统计学意义($P>0.05$)。本研究已获得我院伦理委员会批准。

1.2 方法

对照组采用视网膜光凝术进行治疗,在全身或局部用药控制眼压后,采用氩蓝绿红激光,若为糖尿病视网膜病变患者,光凝部位为后极部颞侧上下血管弓间 5 mm 直径黄斑区的其他各区域。其他病变患者行激光光凝治疗时,选择无灌注区,后极

部光斑控制为 200-300 μm , 周边以及中周部光斑控制为 300-500 μm , 能量、曝光时间、光斑总数分别控制为 260-420 mJ、0.1-0.3s、500-3000 点。观察组视网膜光凝术同对照组,并且在术后 7d,在玻璃体内垂直刺入 TB 针头,将 0.05 mL 雷珠单抗注射液(批准文号:国药准字 S20140003;生产厂家:Novartis Pharma Stein AG;规格:10 mg/mL)缓慢注入。

1.3 观察指标

治疗后,在裂隙灯显微镜下对所有患者虹膜新生血管消退情况进行观察;对比两组虹膜新生血管消退时间和治疗前后静脉循环时间;记录两组不良反应发生情况;所有患者治疗前后均采用非接触式眼压计(日本多美公司生产)对眼压进行测量;通过光学相干断层扫描(Optical coherence tomography, OCT)测定患者视网膜神经纤维层(Retinal nerve fiber layer, RNFL)厚度、围绕视盘中心 3.45mm 直径的视野缺损值。采用 MVIS-2010 型全自动血液流变分析仪(重庆天海医疗设备有限公司)对两组患者治疗前后的血液流变学指标包括血浆黏度(Plasma viscosity, PV)、红细胞压积(Hematocrit, HCT)、血小板黏附率(Platelet adhesion rate, PADT)进行检测比较。分别于玻璃体腔内注射雷珠单抗前和注射后抽取患者的房水样本,以酶联免疫吸附试验法检测患者的房水炎症因子水平包括单核细胞趋化蛋白 1(Monocyte chemoattractant protein 1, MCP-1)、白介素-1 β (Interleukin-1 β , IL-1 β)、白介素-6(Interleukin-6, IL-6)水平,并进行组间比较,检测试剂盒购置于安徽深蓝生物科技有限公司。

1.4 统计学分析

采用 SPSS 20.0 行数据分析。计量资料以($\bar{x}\pm s$)表示,行 t 检验。计数资料以[n(%)]表示,行 χ^2 检验。当 $P<0.05$ 时差异有统计学意义。

2 结果

2.1 两组虹膜新生血管消退时间比较

观察组虹膜新生血管消退时间为(6.02±0.88)d, 短于对照组的(8.96±1.25)d, 两组比较, 差异有统计学意义($t=18.245$, $P=0.000$)。

2.2 两组虹膜新生血管消退情况比较

观察组虹膜新生血管消失率为 95.55%, 高于对照组的 80.00%, 差异有统计学意义($P<0.05$), 见表 1。

表 1 两组虹膜新生血管消退情况比较[n(%)]

Table 1 Comparison of regression of iris neovascularization between the two groups [n(%)]

Groups	Number of eyes	Unchanged	Disappear
Control group	88	17(19.32)	71(80.68)
Observation group	92	4(4.35)	88(95.65)
χ^2		9.781	9.781
P		0.002	0.002

2.3 两组治疗前后 OCT 检查结果比较

两组治疗前视野缺损值、RNFL 厚度比较无统计学差异 ($P>0.05$); 与治疗前对比, 两组治疗后视野缺损值均减小,

RNFL 厚度均增加 ($P<0.05$); 与对照组对比, 观察组治疗后视野缺损值更小, RNFL 厚度更厚 ($P<0.05$), 见表 2。

表 2 两组治疗前后 OCT 检查结果比较($\bar{x}\pm s$)Table 2 Comparison of OCT results between the two groups before and after treatment ($\bar{x}\pm s$)

Groups	Visual field defect value(dB)		RNFL thickness(μm)	
	Before treatment	After treatment	Before treatment	After treatment
Control group(n=88)	19.05 $\pm$ 0.52	16.02 $\pm$ 0.48 [#]	72.15 $\pm$ 2.56	81.16 $\pm$ 3.08 [#]
Observation group(n=92)	19.08 $\pm$ 0.49	13.02 $\pm$ 0.18 [#]	72.19 $\pm$ 2.52	92.05 $\pm$ 3.98 [#]
t	0.398	55.980	0.106	20.466
P	0.691	0.000	0.916	0.000

Note: compared with before treatment, [#] $P<0.05$.

2.4 两组治疗前后眼压、静脉循环时间变化情况比较

两组治疗前静脉循环时间、眼压比较差异无统计学意义 ($P>0.05$); 与治疗前对比, 两组治疗后眼压均降低, 静脉循环

时间均缩短 ($P<0.05$); 与对照组对比, 观察组治疗后眼压更低, 静脉循环时间更短 ($P<0.05$), 见表 3。

表 3 两组治疗前后眼压、静脉循环时间变化情况比较($\bar{x}\pm s$)Table 3 Comparison of intraocular pressure and venous circulation time between the two groups before and after treatment ($\bar{x}\pm s$)

Groups	Intraocular pressure(mmHg)		Venous circulation time(s)	
	Before treatment	After treatment	Before treatment	After treatment
Control group(n=88)	60.98 $\pm$ 0.85	20.69 $\pm$ 0.52 [#]	11.98 $\pm$ 0.85	9.98 $\pm$ 0.55 [#]
Observation group(n=92)	61.02 $\pm$ 0.82	18.02 $\pm$ 0.18 [#]	12.02 $\pm$ 0.82	8.02 $\pm$ 0.19 [#]
t	0.321	46.031	0.321	32.233
P	0.748	0.000	0.748	0.000

Note: compared with before treatment, [#] $P<0.05$.

2.5 两组患者房水炎性因子水平比较

两组患者治疗前房水炎性因子水平比较无统计学差异

($P>0.05$), 治疗后观察组房水炎性因子水平包括 IL-1 β 、IL-6、MCP-1 水平均低于对照组 ($P<0.05$), 见表 4。

表 4 两组患者房水炎性因子水平比较($\bar{x}\pm s$)Table 4 Comparison of the levels of inflammatory factors in aqueous humor between the two groups ($\bar{x}\pm s$)

Groups	IL-1 β (ng/L)		IL-6(ng/L)		MCP-1(ng/L)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group (n=92)	21.87 $\pm$ 3.39	11.25 $\pm$ 2.32 [#]	151.27 $\pm$ 15.59	85.37 $\pm$ 10.12 [#]	241.24 $\pm$ 19.32	146.11 $\pm$ 13.36 [#]
Control group (n=88)	21.07 $\pm$ 3.42	13.97 $\pm$ 2.61 [#]	150.07 $\pm$ 15.11	90.89 $\pm$ 9.92 [#]	243.59 $\pm$ 20.35	154.22 $\pm$ 13.25 [#]
t	1.576	7.397	0.524	3.694	0.795	4.088
P	0.117	0.000	0.601	0.000	0.428	0.000

Note: compared with before treatment, [#] $P<0.05$.

2.6 两组患者血液流变学指标比较

两组患者治疗前各项血液流变学指标比较无统计学差异 ($P>0.05$), 治疗后观察组 PV、HCT、PAAdT 水平均低于对照组 ($P<0.05$), 见表 5。

出现 3 眼点片状结膜下出血, 4 眼结膜水肿, 3 眼前房出血, 不良反应发生率为 10.87%(10/92), 两组不良反应发生率比较差异无明显差异($\chi^2=0.158$, $P=0.691$)。

2.7 两组不良反应发生情况比较

两组患者中对照组出现 2 眼点片状结膜下出血, 3 眼结膜水肿, 3 眼前房出血, 不良反应发生率为 9.09%(8/88), 观察组

3 讨论

新生血管青光眼属于一种病因复杂的眼科疾病, 治疗难度大, 且会严重影响患者视功能^[10,11]。常规眼压控制难以获得理想

表 5 两组患者血液流变学指标比较($\bar{x} \pm s$)Table 5 Comparison of hemorheological indexes between the two groups ($\bar{x} \pm s$)

Groups	PV(mPa / s)		HCT(%)		PAdT(%)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group (n=92)	1.87±0.39	1.25±0.32 [#]	51.87±5.39	35.37±4.12 [#]	41.34±4.82	26.28±3.39 [#]
Control group (n=88)	1.81±0.42	1.37±0.31 [#]	50.97±5.42	39.89±4.42 [#]	42.19±4.93	29.41±3.65 [#]
t	0.994	2.554	1.117	7.100	1.170	5.964
P	0.322	0.011	0.266	0.000	0.244	0.000

Note: compared with before treatment, [#] $P < 0.05$.

的治疗效果,极易造成进行性视功能损伤^[12]。视网膜血管扩张受到各种因素影响,会形成新生血管,导致房角关闭,虹膜新生血管因子生长^[13]。视网膜色素上皮在视网膜光凝术的影响下会有大量尿激酶抑制剂生成,对新生血管生成进行抑制,生成房水的睫状体色素上皮也会被直接破坏,眼底缺氧、缺血状况得以改善^[14]。除此之外,视网膜光凝术治疗还能将视网膜血管无灌注区关闭,促进血液循环进行,确保损伤较小的视网膜细胞获取更多营养,虹膜新生血管也随之消退^[15,16]。虽然视网膜光凝术治疗新生血管青光眼能获得一定效果,但为了进一步提高治疗效果,本研究在此基础上联合雷珠单抗治疗。

本研究发现,观察组虹膜新生血管消失率高于对照组,虹膜新生血管消退时间短于对照组,治疗后眼压低于对照组,静脉循环时间短于对照组,同时两组不良反应发生率比较无统计学差异,提示联合治疗方案治疗新生血管青光眼的疗效理想,且安全性高^[17,18]。究其原因,新生血管青光眼患者因为视网膜缺氧、缺血,进而会大量分泌血管生长因子^[19,20]。雷珠单抗为人源化重组抗血管内皮细胞单克隆抗体片段 Fab 部分,能促进房角、虹膜新生血管消退,使得小梁网滤过功能得到改善,眼压也随之得到改善^[21,22]。OCT 检查能对视网膜内部超微结构进行快速扫描,具有非侵入性、非接触性等特点,在新生血管青光眼诊断与预后判断中具有良好应用价值^[23,24]。本研究中,观察组治疗后视野缺损值小于对照组,RNFL 厚度大于对照组,提示联合视网膜光凝术与雷珠单抗治疗新生血管青光眼能促使视网膜功能与结构得到改善。这可能是因为雷珠单抗能与血管内皮生长因子进行选择性地结合,对房角、虹膜新生血管消退有促进作用;抑制血管内皮生长因子介导的炎症,以此来减少渗漏,促进渗液吸收^[25,26]。在血液流变学指标比较中,观察组患者治疗后的血液流变学指标包括 PV、HCT、PAdT 水平均低于对照组,表明视网膜光凝术联合雷珠单抗治疗新生血管青光眼的效果显著,这是因为雷珠单抗可有效改善患者的眼局部血液循环,畅通原有的血管通路,避免新的血管生成,因此患者的血液流变学指标得以改善^[27,28]。在房水炎症因子水平比较中,治疗后观察组房水炎症因子水平包括 IL-1 β 、IL-6、MCP-1 水平均低于对照组,表明视网膜光凝术联合雷珠单抗治疗新生血管青光眼患者,能够降低机体的炎症反应水平,这是因为应用抗 VEGF 药物雷珠单抗后,前房内的 VEGF 浓度急剧下降,虹膜以及前房角表面的通透性很强的新生血管迅速消退,减少了新生血管内

的 IL-6、IL-8、MCP-1 等炎症因子渗出,因而减少了房水中相关因子的浓度^[29,30]。

综上所述,新生血管青光眼采用视网膜光凝术联合雷珠单抗治疗的疗效理想,可降低房水炎症因子水平,改善患者的血液流变学指标,且安全性高。

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