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雷珠单抗联合复合式小梁切除术及全视网膜光凝术 对新生血管性青光眼患者视功能及房水炎症因子的影响 *

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摘要 目的:探讨复合式小梁切除术及全视网膜光凝术联合雷珠单抗对新生血管性青光眼(NVG)患者视功能及房水炎症因子的影响。**方法:**选取 2017 年 2 月~2019 年 9 月期间我院收治的 NVG 患者 156 例,上述患者根据随机数字表法分为对照组(n=78)和研究组(n=78),对照组患者给予复合式小梁切除术及全视网膜光凝术治疗,研究组则在对照组的基础上联合雷珠单抗治疗,比较两组患者疗效、最佳矫正视力、眼压及房水炎症因子,记录两组患者术后并发症发生率。**结果:**研究组术后 6 个月的临床总有效率为 88.46%(69/78),高于对照组的 67.95%(53/78)($P<0.05$)。研究组术后 1 个月、术后 3 个月、术后 6 个月最佳矫正视力高于对照组,眼压则低于对照组($P<0.05$)。两组患者术后 6 个月单核细胞趋化蛋白 1(MCP-1)、白介素-1 β (IL-1 β)、白介素-6(IL-6)均下降,且研究组低于对照组($P<0.05$)。研究组的并发症总发生率为 8.97%(7/78)低于对照组 21.79%(17/78)($P<0.05$)。**结论:**雷珠单抗联合复合式小梁切除术及全视网膜光凝术治疗 NVG,疗效显著,可有效改善患者视功能及房水炎症因子,同时还可减少术后并发症发生率。

关键词:新生血管性青光眼;雷珠单抗;全视网膜光凝术;视功能;复合式小梁切除术;炎症因子

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The Effect of Combined Trabeculectomy and Panretinal Photocoagulation with Razumab on the Visual Function and Inflammatory Factors of Aqueous Humor in Patients with Neovascular Glaucoma*

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ABSTRACT Objective: To investigate the effect of compound trabeculectomy and retinal photocoagulation combined with leizhumab on the visual function and aqueous inflammatory factors in patients with neovascular glaucoma (NVG). **Methods:** 156 NVG patients in our hospital from February 2017 to September 2019 were selected. The above patients were divided into the control group (n=78) and the study group (n=78) according to the method of random number table. The patients in the control group were treated with compound trabeculectomy and panretinal photocoagulation. The study group was combined with leizhumab on the basis of the control group. The curative effect, the best corrected vision, intraocular pressure and inflammatory factors of aqueous humor between the two groups were compared, the incidence of postoperative complications was recorded. **Results:** The total clinical effective rate of the study group was 88.46% (69/78), which was higher than 67.95% (53/78) of the control group ($P<0.05$). The best corrected visual acuity of the study group was higher than that of the control group at 1 month, 3 months and 6 months after operation, and the intraocular pressure was lower than that of the control group ($P<0.05$). The levels of monocyte chemoattractant protein-1 (MCP-1), interleukin-1 β (IL-1 β), interleukin-6 (IL-6) in the study group were lower than those in the control group ($P<0.05$). The total incidence of complications in the study group was 8.97% (7/78) lower than 21.79% (17/78) in the control group ($P<0.05$). **Conclusion:** Combined trabeculectomy and retinal photocoagulation can improve the visual function and inflammatory factors of aqueous humor, and reduce the incidence of postoperative complications.

Key words: Neovascular glaucoma; Leizhumab; Total retinal photocoagulation; Visual function; Compound trabeculectomy; Inflammatory factors

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前言

新生血管性青光眼(Neovascular glaucoma, NVG)是临床常见的致盲性眼病,可对人体视功能造成不可逆损害^[1,2]。临床最多见的病因是糖尿病视网膜病变和视网膜中央静脉阻塞^[3]。近年来随着糖尿病和血管性疾病患病率的飙升, NVG的发病率也呈逐年递增趋势,现已占据青光眼的30%以上^[4,5]。手术是治疗NVG的常用方法,既往临床常用的手术方式为复合式小梁切除术联合全视网膜光凝术,可在一定程度上阻止疾病进展^[6]。但也常常由于致新生血管因素的持续存在而导致术后治疗效果变差^[7]。雷珠单抗为临床常见的血管内皮生长因子抑制剂,可有效抑制新生血管生成,同时还可诱导新生血管萎缩^[8,9]。本研究通过探讨雷珠单抗联合复合式小梁切除术及全视网膜光凝术对NVG患者视功能及房水炎症因子的影响,以期为临床治疗NVG术式的选择提供参考。

1 资料与方法

1.1 一般资料

选取2017年2月~2019年9月期间我院收治的NVG患者156例,纳入标准:(1)诊断标准参考《中华眼科学第3版》^[10],经裂隙灯显微镜、眼压、视力、房角镜、眼部B超等检查确诊;(2)患者及其家属知情本研究且签署了同意书;(3)术前均积极控制原发病者;(4)使用降眼压药但不能控制至正常者;(5)均为单眼患病者。排除标准:(1)合并有严重心肝肾等重要脏器功能障碍者;(2)妊娠或哺乳期妇女;(3)有视网膜激光光凝治疗、玻璃体注药术等抗青光眼治疗史者;(4)其他类型青光眼病史,如先天性、原发性和外伤性等;(5)不符合手术指征者;(6)伴有眼部外伤史者;(7)精神疾病史者及意识障碍者。根据随机数字表法分为对照组($n=78$)和研究组($n=78$),其中对照组男45例,女33例,年龄41~73岁,平均(52.67 ± 3.95)岁;患眼:左眼41例,右眼37例;体质量指数 $20.2 \sim 27.3 \text{ kg/m}^2$,平均(23.71 ± 0.82) kg/m^2 。研究组男43例,女35例,年龄43~70岁,平均(51.93 ± 4.16)岁;患眼:左眼43例,右眼35例;体质量指数 $21.2 \sim 27.4 \text{ kg/m}^2$,平均(23.54 ± 0.62) kg/m^2 。两组一般资料对比无差异($P>0.05$),均衡可比。此次研究已获得我院医学伦理学委员会批准进行。

1.2 方法

研究组患者给予雷珠单抗联合复合式小梁切除术及全视网膜光凝术治疗,雷珠单抗治疗:常规消毒、铺巾,进针位置取颞下距离角膜缘后3.5~4.0 mm处,随后缓慢推注雷珠单抗(厂家:Novartis Pharma Stein AG,注册证号:S20170004,规格:

10 mg/mL,每瓶装量0.20 mL)0.05 mL,注射完毕后拔出针头,轻按压注射部位30~60s。术毕后,典必舒眼膏涂眼,无菌纱布包扎。雷珠单抗注射治疗5~7d后给予复合式小梁切除术治疗,操作如下:局麻后,以上穹窿为基底做结膜瓣,以角膜缘为基底做巩膜瓣,巩膜厚度为3 mm $\times$ 4 mm 1/2,将0.3 g/L丝霉素棉片放置于巩膜瓣下,于角膜缘2:30位行前房穿刺,放出房水,结束后切除巩膜瓣下小梁组织,大小约为1 mm $\times$ 2 mm,同时行虹膜根切,10/0线间断缝合巩膜瓣,前房、球结膜注入乳酸钠林格氏注射液。术毕后,典必舒眼膏涂眼,无菌纱布包扎。于复合式小梁切除术治疗2周后给予全视网膜光凝术,操作如下:采用532nm半导体激光机(北京镭志威光电技术有限公司),后极部:光斑大小50~150 μm ,能量100~150mW。周边、中周部:光斑大小200~300 μm ,能量150~250mW;曝光时间:0.1~0.15s, III级光斑为宜,总计点数1800~2200点。全视网膜光凝术行3~4次,每次间隔时间5~7d。对照组患者除不给予雷珠单抗治疗外,复合式小梁切除术及全视网膜光凝术操作均同研究组一致。

1.3 观察指标

(1)术后采用门诊复查的方式随访6个月,记录两组患者术后6个月的疗效^[11]。显效:虹膜及前房角的新生血管完全消退,在不给予降眼压药物的情况下,眼压 $\leq 21 \text{ mmHg}$;有效:虹膜及前房角的新生血管明显消退,在给予降眼压药物的情况下,眼压 $\leq 21 \text{ mmHg}$;无效:虹膜新生血管未消退,在给予降眼压药物的情况下,眼压仍高于21 mmHg。总有效率=显效率+有效率。(2)记录两组患者术前、术后1个月、术后3个月、术后6个月的最佳矫正视力、眼压。(3)记录两组术后并发症发生情况。(4)于术前、术后6个月抽取两组患者100 μL 房水,房水取出后迅速移至微量离心管中,避光保存在冰箱(-40°C)中待测。选用上海玉博生物科技有限公司试剂盒,严格遵守试剂盒说明书,采用酶联免疫吸附试验检测单核细胞趋化蛋白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)。

1.4 统计学方法

采用SPSS25.0软件进行统计学分析,计量资料以($\bar{x} \pm s$)表示,比较实施t检验,计数资料以比或率表示,实施卡方检验,检验标准设置为 $\alpha=0.05$ 。

2 结果

2.1 两组疗效比较

研究组术后6个月的临床总有效率为88.46%(69/78),高于对照组的67.95%(53/78)($P<0.05$);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	Effective	Invalid	Total effective rate
Control group($n=78$)	21(26.92)	32(41.03)	25(32.05)	53(67.95)
Study group($n=78$)	29(37.18)	40(51.28)	9(11.54)	69(88.46)
χ^2				10.428
P				0.001

2.2 两组最佳矫正视力、眼压比较

两组术前最佳矫正视力、眼压比较无差异($P>0.05$);两组患者术前、术后1个月、术后3个月、术后6个月最佳矫正视力

呈升高后下降趋势,眼压呈下降后升高趋势($P<0.05$);研究组术后1个月、术后3个月、术后6个月最佳矫正视力高于对照组,眼压则低于对照组($P<0.05$);详见表2。

表2 两组最佳矫正视力、眼压比较($\bar{x}\pm s$)

Table 2 Comparison of the best corrected visual acuity and intraocular pressure between the two groups($\bar{x}\pm s$)

Groups	Best corrected vision				Intraocular pressure(mmHg)			
	Before operation	1 month after operation	3 months after operation	6 months after operation	Before operation	1 month after operation	3 months after operation	6 months after operation
Control group (n=78)	0.39±0.08	1.04±0.19 ^a	0.98±0.15 ^{ab}	0.91±0.16 ^{abc}	43.66±5.74	16.78±3.78 ^a	19.61±4.53 ^{ab}	24.82±4.62 ^{abc}
Study group (n=78)	0.41±0.09	1.24±0.23 ^a	1.13±0.26 ^{ab}	1.01±0.12 ^{abc}	42.93±5.52	13.06±4.39 ^a	15.57±3.69 ^{ab}	18.91±4.21 ^{abc}
t	1.467	5.921	4.413	4.416	0.810	5.671	6.107	8.351
P	0.144	0.000	0.000	0.000	0.419	0.000	0.000	0.000

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

2.3 两组房水炎症因子水平比较

两组患者术前 MCP-1、IL-1 β 、IL-6 比较差异无统计学意义

($P>0.05$);两组患者术后6个月 MCP-1、IL-1 β 、IL-6 均下降,且研究组低于对照组($P<0.05$);详见表3。

表3 两组房水炎症因子水平比较($\bar{x}\pm s$)

Table 3 Comparison of inflammatory factors in aqueous humor between the two groups($\bar{x}\pm s$)

Groups	MCP-1(pg/mL)		IL-1 β (pg/mL)		IL-6(pg/mL)	
	Before operation	6 months after operation	Before operation	6 months after operation	Before operation	6 months after operation
Control group (n=78)	3021.87±283.22	2632.71±274.26 ^a	22.68±4.71	18.02±2.57 ^a	192.23±18.97	134.21±25.89 ^a
Study group(n=78)	3049.26±314.20	2093.60±286.17 ^a	22.32±3.74	14.11±2.47 ^a	190.18±24.86	85.43±19.75 ^a
t	0.572	12.012	0.529	9.688	0.579	13.230
P	0.568	0.000	0.598	0.000	0.563	0.000

2.4 两组并发症发生率比较

研究组的并发症总发生率为 8.97%(7/78) 低于对照组的

21.79%(17/78),差异有统计学意义($P<0.05$);详见表4。

表4 两组并发症发生率比较【例(%)】

Table 4 Comparison of the incidence of complications between the two groups[n(%)]

Groups	Corneal edema	Anterior exudation	Eyeball pain	Anterior chamber / vitreous hemorrhage	Total incidence rate
Control group(n=78)	3(3.85)	3(3.85)	5(6.41)	6(7.69)	17(21.79)
Study group(n=78)	1(1.28)	2(2.56)	2(2.56)	2(2.56)	7(8.97)
χ^2					4.789
P					0.029

3 讨论

NVG 是临床常见的难治性青光眼,该病可随着纤维血管组织的生长,进而减少甚至抑制房水流出,造成房角关闭、角膜内皮增生,最终引起机体眼压升高,并会造成不可逆的视力丧失,甚至摘除眼球^[12-14]。现临床针对 NVG 的治疗多以抗青光眼手术、治疗原发病、激光等疗法为主,复合式小梁切除术是治疗 NVG 的常用手段,但其手术成功率仅为 11%~33%,这主要是

因为复合式小梁切除术仅能缓解临床症状,无法从根本上解决视网膜缺血缺氧这一病理问题,导致新生血管形成纤维膜会继续堵塞滤过道,再一次影响房水排出^[15-17]。全视网膜光凝术通过激光光凝视网膜的无灌注区域,来避免形成血管,以改善视网膜缺血缺氧状况,提高手术治疗效果^[18,19]。但全视网膜光凝术同样也属于治标不治本类治疗。NVG 的发病机制复杂,有学者认为视网膜缺血导致血管生成因子的释放在 NVG 的发病过程中发挥重要作用^[20]。眼部在缺血缺氧状态下,可使视网膜分泌血

管生成因子,进而导致微血管扩张、通透性增强,随着新生血管膜跨越前房角,房水无法排出,眼压增高,最终形成青光眼^[21]。因此,阻断血管生成因子的分泌,对于靶向治疗 NVG 有重要价值。雷珠单抗是一种新型抗血管生成因子类药物,可促进新生血管萎缩及抑制瘢痕形成,近年来已逐渐应用于眼科疾病的治疗中^[22]。

本次研究结果显示,研究组术后 6 个月的疗效、最佳矫正视力、眼压改善均优于对照组,可见在复合式小梁切除术及全视网膜光凝术治疗的基础上联合雷珠单抗治疗,可有效阻止疾病进展,改善患者预后。雷珠单抗进入人体后可非特异性的与 VEGF-A 结合,阻断血管生成因子与其受体的结合途径,利于新生血管消退,同时还可促进新生血管萎缩,对接下来的复合式小梁切除术创造有利条件,提高手术成功率;此外,雷珠单抗还可调控视网膜-血屏障的通透性,便于促进视网膜内渗液吸收,维持或提高患者视功能^[23-25]。复合式小梁切除术治疗可抑制纤维细胞增殖及瘢痕形成,并建立良好的房水引流通路,缓解机体高血压情况,减轻高血压对人体视神经的损害;全视网膜光凝术可封闭视网膜血管无灌注区,预防再次生成新生血管,进一步加强手术治疗效果;由于 NVG 患者眼部大量新生血管生成,且此类新生血管极其"不健康",血管通透性增加,可导致大量细胞因子从这些"不健康"的血管中渗出,引起机体炎症反应^[26-28]。本研究中两组患者房水炎症因子水平均有所下降,且雷珠单抗联合复合式小梁切除术及全视网膜光凝术治疗者效果更佳。这可能是因为雷珠单抗可有效降低前房内的血管生成因子浓度,促使虹膜以及前房角表面通透性很强的血管迅速消退,减少了上述炎症因子的渗出,从而减轻机体炎症反应^[29,30]。另研究组的并发症总发生率低于对照组,可见本次联合治疗方案安全性较好。这主要是因为雷珠单抗可最大限度保护患者视功能,降低眼压,减少新生血管生成,从而减少手术并发症。

综上所述,雷珠单抗联合复合式小梁切除术及全视网膜光凝术治疗 NVG,疗效显著,可有效改善患者视功能及房水炎症因子,同时还可减少术后并发症发生率。

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