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雷珠单抗与阿柏西普玻璃体腔注射治疗渗出性年龄相关性黄斑变性的疗效观察 *

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摘要 目的:探究雷珠单抗与阿柏西普玻璃体腔注射治疗渗出性年龄相关性黄斑变性的临床疗效与安全性。**方法:**选取 2015 年 5 月~2018 年 5 月我院收治的渗出性年龄相关性黄斑变性患者 98 例(98 眼),采用随机数字表法将患者分为两组,A 组玻璃体腔内缓慢注射 0.05 mL(0.5 mg)雷珠单抗注射液,B 组玻璃体腔内缓慢注射 0.05 mL(2 mg)阿柏西普注射液。比较两组患者的视力改善情况、眼动脉血流动力学、黄斑中心凹视网膜厚度及不良反应的发生情况。**结果:**治疗前两组患者的视力比较无统计学差异($P>0.05$),治疗后,B 组视力显著高于 A 组($P<0.05$);。两组患者治疗前后眼动脉血流动力学相关指标比较均无统计学差异($P>0.05$)。;两组患者治疗后的黄斑中心凹视网膜厚度均显著降低,且治疗 3 个月 B 组治疗 3 个月显著低于 A 组($P<0.05$);B 组患者注射药物后结膜下大出血发生率显著低于 A 组($P<0.05$)。**结论:**阿柏西普可显著改善渗出性年龄相关性黄斑变性患者的视力,且安全性高,可能与其可显著改善患者的黄斑中心凹视网膜厚度有关,且不良反应发生率低,安全性好。

关键词:雷珠单抗;阿柏西普;玻璃体腔注射;渗出性年龄相关性黄斑变性

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Observation on the Therapeutic Effect of Lucentis and Aflibercept Intravitreal Injection in the Treatment of Exudative Age-related Macular Degeneration*

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ABSTRACT Objective: To investigate the efficacy and safety of intravitreal injection of lucentis and aflibercept in the treatment of exudative age-related macular degeneration. **Methods:** 98 cases of patients (98 eyes) with exudative age-related macular degeneration admitted to our hospital from May 2015 to May 2018 were enrolled and divided into two groups by the random number table. Group A was slowly injected in the vitreous cavity with 0.05 mL (0.5 mg) of ranibizumab injection, 0.05 mL (2 mg) of aboxicept was slowly injected into the vitreous cavity of group B. The vision improvement, ocular arterial hemodynamics, macular foveal retinal thickness and adverse reactions were compared between the two groups. **Results:** There was no significant difference in vision between the two groups before treatment ($P>0.05$). After treatment, the vision of group B was significantly higher than that of group A ($P<0.05$). There was no statistical difference in the ocular arterial hemodynamics between the two groups before and after treatment($P>0.05$). The thickness of foveal retinal fove after treatment was significantly lower in both groups, and it was significantly lower in the group B than that in the group A ($P<0.05$). The incidence of subconjunctival hemorrhage was significantly lower in the group B than that in the group A ($P<0.05$). **Conclusion:** Aflibercept can significantly improve the vision of patients with exudative age-related macular degeneration with high safety, which may be related to the significantly improvedment of macular fovea retinal thickness, and the incidence of adverse reactions is low and the safety is good.

Key words: Lucentis; Aflibercept; Intravitreal injection; Exudative age-related macular degeneration

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前言

年龄相关性黄斑变性是一种老年人常见的疾病，好发于 50 岁以上老人,可双眼同时或者先后发病,严重影响患者的视功能,是老年患者致盲的首要因素[1-3]。随着我国老龄化的加剧,该病的发病率呈现逐年上升的态势。该病根据临床表现分为萎缩性和渗出性两种类型,萎缩性主要表现为视网膜色素上皮和脉络膜毛细血管萎缩、玻璃体增厚而引起的视网膜黄斑区域的萎缩[4,5]。渗出性主要表现为脉络膜出现新生血管、玻璃体遭到破坏,视网膜色素上皮脱落或纤维化[6,7]。该病的发病机制目前

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尚不清楚，主要有氧化损伤、遗传、视网膜色素上皮细胞衰老和血管模式等学说[8,9]。有研究显示[10]，约 90%的渗出性年龄相关性黄斑变性患者视力丧失是由于脉络膜新生血管造成的。患者光感受器外节反复脱落、变性和再次合成导致代谢应激，促进脉络膜新生血管的形成。

临床对渗出性年龄相关性黄斑变性于该病的治疗，包括光动力学疗法、激光疗法和经瞳孔温热疗法，但均无法改善或者患者的视力[11-13]。而抗血管内皮生长因子药物是一种新的趋势，已被证实在脉络膜新生血管形成中具有重要作用，为改善渗出性年龄相关性黄斑变性患者的视力带来了希望[14-16]。雷珠单抗与阿柏西普均为抗血管内皮生长因子药物[17,18]，本文研究主要比较了两二者对于渗出性年龄相关性黄斑变性患者的治疗效果和安全性，以期为临床治疗提供参考。

1 资料和方法

1.1 一般资料

研究时间段为 2015 年 5 月 ~2018 年 5 月，选取我院 2015 年 5 月 ~2018 年 5 月收治的渗出性年龄相关性黄斑变性患者 98 例(98 眼)，纳入标准：① 所有患者均经眼底荧光造影确诊；② 所有患者均为单眼病变；③ 均出现视力下降、眼前黑影和视力模糊等症状；④ 年龄大于 55 岁。排除标准：① 既往有眼部手术史或眼底病史者；② 合并其他眼部病变者；③ 合并严重高血压、高度近视和糖尿病者；④ 入组前使用其他抗新生血管治疗者。采用随机数字表法将患者分为两组，A 组 49 例，男 28 例，女 21 例；年龄 55~70 岁，平均 64.25± 3.12 岁；病程 10d~24 个月，平均 5.12± 1.05 个月；左眼 31 例，右眼 18 例。；B 组 49 例，男 27 例，女 22 例；年龄 55~68 岁，平均 63.87± 3.12 岁；病程 8d~24 个月，平均 5.01± 0.97 个月；左眼 29 例，右眼 20 例。两组一般资料比较差异均无统计学意义(P>0.05)，具有可比性。

1.2 治疗方法

患者均于术前给予盐酸左氧氟沙星滴眼液预防感染、玻璃体内注射前给予盐酸丙美卡因滴眼液，完成表面麻醉之后，用 5 g/L 的碘伏冲洗结膜囊，在无菌层流手术室内进行常规术前消毒，用齿镊固定患者的眼球，于距离角巩膜缘后 3.5 mm 睫状体部位进针，深度约为 4~6 mm，针头指向玻璃体中央。A 组缓慢注射 0.05 mL(0.5 mg)雷珠单抗注射液(Novartis Pharma Schweiz AG，S20181010)，每 4 周注射 1 次。B 组缓慢注射 0.05 mL(2 mg)阿柏西普注射液(Bayer Australia Ltd，S20180001)，前三个月每 4 周注射 1 次，之后每 8 周注射 1 次。两组均治疗 5 个月。

1.3 观察指标

① 两组患者治疗前后视力情况比较，：采用国际标准对数视力表对两组患者治疗前、治疗 1 个月和治疗 3 个月的最佳矫正视力进行比较。② 治疗前后比较两组患者的眼血流动力学：采用 Logiq7 型采用超声诊断仪(德国 GF 公司生产)于术前、术后 1 周和 4 周进行检查，患者取平卧位，探头频率：4~12 MHz，声速与血管角小于 20°，将探头轻触患者的上脸，水平扫描，在球后 15~20 mm 范围进行眼动脉血流频谱和参数测量。包括收缩期峰值流速(PSV)、舒张末期血流速度(EDV)和阻力指数(RI)、搏动指数(PI)。③ 治疗前后比较两组患者的黄斑中心凹视网膜厚度，：采用 SPECTRALIS-OCT 仪(德国 Heidelberg 公司生产)对两组患者治疗前、治疗 1 个月和治疗 3 个月的黄斑中心凹视网膜厚度进行检测。④ 比较两组患者的不良反应发生情况。

1.4 统计学方法

采用 SPSS16.0 对数据进行统计学分析，计数资料以率(%)表示，组间比较行卡方检验，计量资料以($\bar{x}\pm s$)表示，组间比较行 t 检验，以 P<0.05 为差异有统计学意义。

2 结果

2.1 两组治疗前后视力的比较

治疗后，观察组视力显著高于对照组(P＜0.05)，见表 1。

表 1 两组患者治疗前后视力的比较($\bar{x}\pm s$)

Table 1 Comparison of the vision before and after treatment between two groups($\bar{x}\pm s$)

Groups	Cases	Before treatment	After treatment	t	P
Group A	49	0.15± 0.03	0.26± 0.06	-10.111	＜0.001
Group B	49	0.16± 0.04	0.29± 0.07	11.287	＜0.001
t	-	-1.400	2.278	-	-
P	-	0.165	0.025	-	-

2.2 两组治疗前后眼动脉血流动力学的比较

两组治疗前后眼动脉血流动力学相关指标比较均无统计学差异(P＞0.05)，见表 2。

2.3 两组治疗前后黄斑中心凹视网膜厚度的比较

两组治疗后黄斑中心凹视网膜厚度均较治疗前显著降低，且治疗 3 个月观察组治疗 3 个月黄斑中心凹视网膜厚度显著低于对照组(P＜0.05)，见表 3。

2.4 两组不良反应发生情况的比较

两组患者在治疗期间均未出现神经体统及过敏等不良反应，A 组患者出现 11 例注射药物后第二天结膜下大出血，B 组出现 3 例，B 组结膜下大出血的发生率显著低于 A 组两组间比较具有统计学差异(χ^2=5.333，P=0.021)。

3 讨论

渗出性年龄相关性黄斑变性是黄斑区域结构的衰老性改变，表现为视网膜色素上皮细胞对视细胞外节盘吞噬能力下降，使得未被完全消化的盘膜残留于基底部细胞中，并向细胞外排出并沉积于玻璃体，形成玻璃膜疣，引起脉络毛细血管通过破裂的玻璃膜进入视网膜神经上皮下，进而形成脉络膜新生血管[19-21]。随着目前渗出性年龄相关性黄斑变性患者的日益增

多，医疗技术的不断发展，抗血管内皮生长因子药物已从抗肿瘤治疗扩展到了眼科疾病领域，成为治疗渗出性年龄相关性黄斑变性的一种新方法[22,23]。因此，本文主要针对两种抗血管内皮生长因子 -A(VEGF-A)药物的治疗效果进行对比研究。

表 2 比较 两组患者的治疗前后眼动脉血流动力学的比较($\bar{x}\pm s$)

Table 2 Comparison of the ophthalmic arterial blood flow mechanics between two groups before and after treatment($\bar{x}\pm s$)

Groups	Cases	Before operation	1 week after operation	4 week after operation
Group A(n=49)	PSV	15.56± 2.57	15.84± 2.63	16.25± 3.02
	EDV	7.89± 2.11	8.06± 2.31	8.22± 2.42
	PI	2.01± 0.54	0.98± 0.31	1.95± 0.28
	RI	0.83± 0.21	0.78± 0.18	0.77± 0.17
Group B(n=49)	PSV	2.55± 0.62	1.58± 0.41	1.77± 0.48
	EDV	15.35± 2.45	15.76± 2.65	16.13± 2.87
	PI	7.91± 2.23	8.01± 2.12	8.13± 2.21
	RI	0.85± 0.23	0.79± 0.19	0.76± 0.15

表 3 两组治疗前后黄斑中心凹视网膜厚度的比较($\bar{x}\pm s$)

Table 3 Comparison of the macular fovea thickness between two groups before and after treatment($\bar{x}\pm s$)

Groups	Cases	Before treatment	Treatment 1 month	Treatment 3 month
Group A	49	414.32± 98.25	358.34± 75.21*	319.58± 68.27*
Group B	49	408.56± 95.37	336.85± 70.12*	274.62± 65.24*
t		0.294	1.463	3.333
P		0.769	0.147	0.001

注：与治疗前相比，*$P<0.05$。

Note：Compared with before treatment, *$P<0.05$.

阿柏西普于 2011 年由美国 FDA 批准用于治疗渗出性年龄相关性黄斑变性，是一种人源抗血管内皮生长因子受体融合蛋白，可与所有 VEGF-A 及胎盘生长因子 (PIGF) 结合，而 VEGF-A 及 PIGF 可促进内皮细胞的分裂、趋化，并增加血管的通透性和血管新生[24,25]。阿柏西普通过与 VEGF-A 及 PIGF 结合抑制其结合并激活血管内皮生长因子受体，从而抑制脉络膜的血管新生[26,27]。有研究显示[28]，阿柏西普能够防止可分泌血管内皮生长因子的转基因小鼠脉络膜新生血管膜的增殖，还能阻止角膜新生血管的发生。雷珠单抗是第二代人源化抗血管内皮生长因子药物，具有减轻黄斑水肿、改善视力、缩小新生血管渗漏的作用[29]。有研究显示[30]，单纯玻璃体注射雷珠单抗可显著减轻患者的脉络膜渗漏，改善视力。本研究结果显示，治疗 3 个月 B 组患者治疗 3 个月的黄斑中心凹视网膜厚度显著低于 A 组，且 B 组患者的视力恢复情况显著优于 BA 组。说，表明阿柏西普可显著改善渗出性年龄相关性黄斑变性患者的视力，临床效果较好。这可能与阿柏西普可与所有类型的 VEGF-A 及 PIGF 结合，亲和力远远高于雷珠单抗，且结合时间较长有关[31]。在不良反应方面，该类药物主要包括抗玻璃体腔注射操作相关并反症和药物本身的不良反应。药物本身的不良反应主要有玻璃体炎、虹膜炎、血压升高、脑血管意外、皮肤过敏等。本研究中，B 组注射药物后第二天结膜下大出血的发生率显著低于 A 组，说明阿柏西普的注射相关不良反应较小安全性更高。这可能与阿柏西普给药间隔时间长，减少了注射次数有关。

综上所述，阿柏西普可显著改善渗出性年龄相关性黄斑变性患者的视力，且安全性高，可能与其可显著改善患者的黄斑中心凹视网膜厚度有关阿柏西普可显著改善渗出性年龄相关性黄斑变性患者的视力，可能与其可显著改善患者的黄斑中心凹视网膜厚度有关，但具体的且作用机制有待进一步研究。且阿柏西普的玻璃体注射操作不良反应发生率低，安全性好。

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