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康柏西普与雷珠单抗对年龄相关性黄斑变性患者血清 CRP、VEGF、眼压及视力的影响

魏艳丽 冉莉君 廖洪霞 陈少琼 叶 剑△

（第三军医大学大坪医院野战外科研究所眼科 重庆 400032）

摘要 目的：探讨康柏西普与雷珠单抗对年龄相关性黄斑变性（AMD）患者血清中 C 反应蛋白(CRP)、血管内皮生长因子（VEGF）水平、眼压（IOP）及视力的影响。**方法**：选取 2015 年 4 月到 2016 年 5 月在我院接受治疗的 AMD 患者 70 例作为研究对象，采用随机数字表法将所有患者分为观察组和对照组各 35 例，所有患者给予内眼手术标准玻璃体注射治疗，观察组给予康柏西普注射液 1.5mg 腔内注射，对照组给予雷珠单抗注射液 0.5 mL 腔内注射，对比两组患者治疗前、治疗后 3d 血清 CRP、VEGF 水平；记录并对比两组患者视力、IOP 水平及并发症情况。**结果**：两组患者治疗后 3d 血清 CRP、VEGF 水平较治疗前下降，且观察组患者 CRP、VEGF 水平低于对照组（P<0.05）；两组患者治疗后 3d 视力最小视角对数（logMAR）及 IOP 较治疗前降低，且观察组患者视力 logMAR 及 IOP 水平明显低于对照组，差异均有统计学意义（P<0.05）。治疗后 3d，两组各出现 1 例玻璃体出血，并发症发生率比较差异无统计学意义（P>0.05）。**结论**：相对于雷珠单抗，康柏西普更能有效降低 AMD 患者血清 CRP、VEGF 水平和 IOP，提高患者视力，改善病情，值得临床推广应用。

关键词：康柏西普；雷珠单抗；年龄相关性黄斑变性；眼压；视力

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Effects of Conbercept and Ranibizumab on Serum Levels of CRP, VEGF, Intraocular Pressure and Visual Acuity in Patients with Age-Related Macular Degeneration

WEI Yan-li, RAN Li-jun, LIAO Hong-xia, CHEN Shao-qiong, YE Jian△

(Department of Ophthalmology, Research Institute of Surgery,

Daping Hospital of Third Military Medical University, Chongqing, 400032, China)

ABSTRACT Objective: To investigate the effects of conbercept and ranibizumab on serum levels of C reactive protein (CRP), vascular endothelial growth factor (VEGF), intraocular pressure (IOP) and visual acuity in patients with age-related macular degeneration (AMD). **Methods:** A total of 70 patients with AMD, who were treated in Daping Hospital of Third Military Medical University from April 2015 to May 2016, were selected and randomly divided into observation group(n=35) and control group (n=35). All patients were treated with standard vitreous injection for intra ocular surgery, the observation group was treated with 1.5 mg conbercept injection by intrapleural injection,and the control group was treated with 0.5 mL ranibizumab injection by intrapleural injection. The serum levels of CRP and VEGF of the two groups before treatment and 3d after treatment were compared, the visual acuity, data of IOP and complications were recorded and compared between the two groups. **Results:** The serum levels of CRP and VEGF in the two groups 3d after treatment were significantly lower than those before treatment, and the serum levels of CRP and VEGF in the observation group were significantly lower than those in the control group(P<0.05). The visual acuity minimum visual angle (logMAR) and IOP of the two groups 3d after treatment were lower than those before treatment, the visual acuity logMAR and IOP in the observation group were significantly lower than those in the control group, the difference was statistically significant (P<0.05). There was 1 case of vitreous hemorrhage in each group 3d after treatment, but there was no significant difference in the incidence of complications (P>0.05). **Conclusion:** Compared with ranibizumab, conbercept can effectively reduce the serum levels of CRP, VEGF and IOP in the patients with AMD,improve visual acuity and the patient's condition, which is worthy of clinical application.

Key words: Conbercept; Ranibizumab; Age-related macular degeneration; Intraocular pressure; Visual acuity

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前言

年龄相关性黄斑变性（age-related macular degenration，AMD）是一种黄斑区结构衰老性病变的疾病，中老年人是其主

作者简介：魏艳丽（1976-），女，硕士，主治医师，从事眼底病方面的研究，E-mail: yevgtd@163.com

△ 通讯作者：叶剑（1961-），男，博士，主任医师，从事白内障方面的研究，E-mail: cduaui@163.com

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要发病人群[1,2]。随着近年来人口老龄化的加快,AMD 的发病率也呈逐年上升趋势。AMD 是导致老年人失明的重要疾病之一,严重影响患者生活质量[3,4]。AMD 分为萎缩型和渗出型两类,萎缩型又称干性,主要特征为进行性色素上皮萎缩,进而导致黄斑区萎缩变性;渗出型又被称为湿性,主要表现为玻璃膜遭到破坏和视网膜下新生血管的形成,其主要病理特征是视网膜色素上皮出血性盘状脱离[5,6]。早期诊断和合理的治疗能有效控制病情,以往手术治疗是 AMD 患者临床治疗的主要手段,但由于病情复杂及老年患者手术耐受力差,导致手术风险较高,因此药物治疗 AMD 显得尤为重要[7,8]。湿性 AMD 对视力的损伤程度远大于干性 AMD,脉络膜新生血管是导致视力下降甚至完全失明的主要因素,血管内皮生长因子(vascular endothelial growth factor,VEGF)类药物能阻止病理性新生血管的形成,VEGF 抑制剂能有效改善 AMD 患者的病情,极大程度降低致盲率[9,10]。康柏西普和雷珠单抗是临床常见的 VEGF 抑制剂,但关于康柏西普与雷珠单抗对 AMD 患者炎症因子、VEGF 影响的报道甚少,因此本文通过研究康柏西普与雷珠单抗对 AMD 患者血清 C 反应蛋白(C-reactionprotein,CRP)、VEGF、眼压及视力的影响,以期为临床治疗 AMD 选择合适的用药方案提供指导,现报道如下。

1 资料与方法

1.1 一般资料

选取 2015 年 4 月到 2016 年 5 月在我院接受治疗的 AMD 患者 70 例作为研究对象,纳入标准:(1)患者均为单眼病变;(2)年龄均大于等于 60 岁;(3)经眼科常规检查、光学断层扫瞄及眼底荧光造影确诊为 AMD 患者,均符合《老年性黄斑变性临床诊断标准》[11];(4)患者治疗依从性高,家属签署知情同意书。排除标准:(1)糖尿病、高血压等相关视网膜病变患者;(2)合并严重肝肾功能障碍者;(3)合并青光眼、白内障患者;(4)精神病患病史无法正常交流者;(5)既往接受手术或药物治疗患者。采用随机数字表法将所有患者分为观察组和对照组各 35 例,观察组男 18 例,女 17 例,年龄 60-80 岁,平均年龄(63.03± 6.19)岁,病程 8-30 个月,平均病程(18.21± 5.01)个月。对照组男 19 例,女 16 例,年龄 61-81 岁,平均年龄(64.28± 7.03)岁,病程 9-31 个月,平均病程(17.68± 5.37)个月。两组患者的一般资料无明显差异(P＞0.05),具有可比性。

1.2 方法

所有患者给予内眼手术标准玻璃体注射治疗,术前连续 3d 给予乐必妥眼液滴眼,术前 1d 给予碘伏冲洗结膜囊,术前常规消毒铺布,5%托吡卡胺用于散瞳,使用盐酸利多卡因进行麻醉,术中用 18G 钝针头专用滤过取液针抽取对应药量,在颞骨上方角膜缘外 3.5 mm 处垂直巩膜面刺入眼内缓慢注入玻璃体腔,观察组给予康柏西普注射液(国药准字 S20130012,成都康弘生物科技有限公司)1.5 mg 腔内注射,对照组给予雷珠单抗注射液(S20160002,Novartis Pharma Schweiz AG)0.5 mL 腔内注射,拔出针头按压 30s 防止返流,术后常规包眼,两组患者均每月注射一次,连续治疗 3 个月。

1.3 观察指标

1.3.1 血清学指标检测 在治疗前和治疗后 3d 采集所有研究对象空腹 12 h 空腹静脉血 5 mL,3000 r/min 离心 10 min,分离血清后放入 -70℃冰箱保存,采用免疫速率散射比浊法检测血清 CRP 水平,使用美国宝特 ELX-808 酶标仪,通过双抗体夹心酶联免疫吸附法(ELISA)检测血清中 VEGF 水平,试剂盒购于康肽生物科技(北京)有限公司,操作均按说明书指导进行。

1.3.2 视力检查 治疗前和治疗后 3d 对所有研究对象的裸眼视力进行常规检查记录,采用 5%复方托吡卡胺滴眼液散瞳进行检影验光确定,并转换为最小视角对数(logMAR)进行实例分析。

1.3.3 眼压检查 采用日本 Topcon 非触接式眼压计检查所有研究对象治疗前和治疗后 3d 的眼内压(IOP)。

1.3.4 并发症观察 观察两组患者疗过程中精神疾病、神经系统疾病的发生情况,以及治疗后 3d 玻璃体出血、白内障、眼内炎视网膜脱落及心血管疾病等并发症情况。

1.4 统计学方法

所有数据均用 SPSS19.0 进行统计分析,计数资料以率(%)的形式表示,采用卡方检验,计量资料以($\bar{x}\pm s$)的形式表示,采用 t 检验,以 P<0.05 为差异有统计学意义。

2 结果

2.1 两组患者血清学指标对比

两组患者治疗前血清中 CRP、VEGF 比较无统计学意义(P>0.05);两组患者治疗后 3d 血清中 CRP、VEGF 水平较治疗前下降,且观察组患者 CRP、VEGF 水平显著低于对照组,差异均有统计学意义(P<0.05),详见表 1。

表 1 两组患者治疗前后血清中 CRP、VEGF 水平对比($\bar{x}\pm s$)

Table 1 Comparison of serum CRP and VEGF levels between two groups before and after treatment

Groups	n	Time	CRP(mg/L)	VEGF(ng/L)
Control group	35	Before treatment	9.43± 1.33	154.69± 23.68
		3d After treatment	7.51± 1.10#	94.21± 14.99#
Observation group	35	Before treatment treatment	9.50± 1.21	152.97± 24.07
		3d After treatment	6.19± 0.71#*	72.33± 11.65#*

Note: Compared with before treatment,# P<0.05; Compared with the control group, *P<0.05.

2.2 两组患者视力及眼压指标对比

两组治疗前视力 logMAR 及 IOP 比较差异无统计学意义(P>0.05);两组患者治疗后 3d 视力 logMAR 及 IOP 较治疗前降低,且观察组患者视力 logMAR 及 IOP 明显低于对照组,差

异均有统计学意义(P<0.05),详见表 2。

表 2 两组患者治疗前后视力及眼压对比($\bar{x}\pm s$)

Table 2 Comparison of visual acuity and intraocular pressure between two groups before and after treatment($\bar{x}\pm s$)

Groups	n	Time	logMAR	IOP(mmHg)
Control group	35	Before treatment	0.701± 0.088	15.38± 2.62
		3d After treatment	0.491± 0.651#	14.25± 1.78#
Observation group	35	Before treatment	0.699± 0.076	15.61± 2.53
		3d After treatment	0.353± 0.039#*	12.06± 1.52#*

Note: Compared with before treatment, # P<0.05; compared with the control group, *P<0.05.

2.3 两组并发症比较

两组患者治疗过程中均未出现精神疾病、神经系统疾病,治疗后 3d 两组各出现 1 例玻璃体出血,经对症治疗后均缓解,白内障、眼内炎视网膜脱落及心血管疾病等恶性并发症均未出现,两组并发症发生率均为 2.86%,比较差异无统计学意义(x^2=0.000,P=1.000)。

3 讨论

AMD 是导致老年患者视力下降甚至失明的重要疾病,双眼同时或先后发病,病变初期无明显临床特征,视物时可察觉有暗点,单眼发病与其他眼部疾病相似易被忽视,导致延误治疗,病情后期会引起视力进行性损害,严重影响老年患者生活质量[12-14]。随着人口老龄化趋势上升,AMD 的发病趋势也日渐上升,因此早期诊断和合理治疗迫在眉睫[15]。AMD 发病机制尚未确定,可能受遗传、慢性光损害、营养障碍、中毒、免疫性疾病、心血管及呼吸系统等全身性疾病等影响,在众多危险因素的影响下,导致色素上皮层新生血管过度活跃,脉络膜新生血管化,进而导致局部视网膜渗血、瘢痕以及渗出形成,若出现瘢痕扩大,还可导致色素及神经上皮脱落,严重损害患者的视力[16-18]。由此可见,AMD 的主要发病机制是脉络膜新生血管,因此抑制新生血管可作为治疗 AMD 的切入点。

雷珠单抗和康柏西普是临床上较为常见的抗 VEGF 药物,雷珠单抗是专为眼科设计的重组单克隆抗体片段(Fab),可以抑制新生血管形成,降低由血管渗漏引起的渗出、水肿及炎症反应,然而雷珠单抗价格昂贵,患者多次治疗需承担较重的经济负担[19,20]。本次研究结果显示,两组患者治疗后 3d 血清中 VEGF 水平显较治疗前下降,且观察组患者 VEGF 水平显著低于对照组,差异均有统计学意义(P<0.05),说明相对于雷珠单抗注射液,康柏西普注射液能更有效的抑制 AMD 患者 VEGF 分泌合成,阻止血管新生。VEGF 是一种具有强大促血管生成功能的因子,与新生血管的生成有直接的联系,色素上皮层新生血管活跃过度可增加 AMD 的发生率,因此 VEGF 水平可影响 AMD 的发生、发展[21,22]。分析原因康柏西普是我国研发的抗 VEGF 药物,可以与 VEGF 受体竞争性结合,有效阻止 VEGF 发挥作用,防止病理性新生血管的形成[23-25]。

AMD 属于渗出性疾病,因此 AMD 程度与炎症反应关联密切[26]。CRP 是炎症反应的重要指标,人体处于正常状态时,血清中 CRP 属于偏低浓度,CRP 浓度会随着人体受到创伤或刺激等导致人体状态不正常的因素而上升,相关研究表明在黄斑变性组织病理切片中可发现大量的免疫活性细胞、巨噬细胞及淋巴细胞等炎性细胞,且炎性细胞的数量直接影响病程轻重,病程越严重,炎性细胞越多[27,28]。本研究结果显示,两组患者治疗后 3d 血清中 CRP 水平较治疗前下降,且观察组患者 CRP 水平显著低于对照组,差异均有统计学意义(P<0.05),说明康柏西普能更有效的抑制 AMD 患者的炎症反应,改善病情。本研究结果还显示两组患者治疗后视力及眼压较治疗前有明显好转,且观察组患者治疗后 3d 视力 logMAR 及 IOP 明显低于对照组,说明康柏西普治疗 AMD 能显著提高患者视力,降低眼压恢复视网膜结构,致盲率风险显著下降。视力 logMAR 是最小分辨角的对数表达,即数值越小,视力越好,IOP 是一个衡量眼内压力的参考值,正常的 IOP 对维持眼球形态、保持眼睛的正常生理功能具有重要的作用[29]。康柏西普主要是通过抑制 VEGF 生成来治疗 AMD 患者,患者疾病得到控制后眼内房水含量也相对降低,进而降低眼压[30]。治疗后两组各出现 1 例玻璃体出血,对症治疗后很快缓解,这说明两种治疗方法并发症均较少且症状轻微,用药相对安全。

综上所述,相对于雷珠单抗,康柏西普更能有效降低 AMD 患者血清中 CRP、VEGF 水平以及眼压,提高患者视力,改善病情,值得临床推广应用。

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