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曲伏前列腺素滴眼液对原发性开角型青光眼患者眼压、血流动力学及ET-1、TIMP-2的影响

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摘要 目的：探讨曲伏前列腺素滴眼液对原发性开角型青光眼（POAG）患者眼压、血流动力学及内皮素-1（ET-1）、基质金属蛋白酶-2抑制因子（TIMP-2）的影响。**方法：**选取2015年2月至2017年2月我院眼科收治的70例患者，按照随机数字表法分为对照组和观察组，每组各35例，对照组和观察组患者分别给予马来酸噻吗洛尔滴眼液和曲伏前列腺素滴眼液治疗，治疗周期为3个月。对比分析治疗前、治疗4周、8周及12周后两组患者的平均眼压（IOP）、昼夜IOP差，并对比治疗前、治疗12周后的睫状后动脉（PCA）、视网膜中央动脉（CRA）、收缩期峰值血流速度（PSV）、舒张末期血流速度（EDV）、血管阻力指数（RI）、血浆ET-1及房水TIMP-2的改善情况。**结果：**治疗前两组患者平均IOP、昼夜IOP差、PCA和CRA血流动力学、血浆ET-1及房水TIMP-2差异无统计学意义（P＞0.05）；治疗4周、8周、12周后，两组平均IOP、昼夜IOP差明显低于治疗前，且治疗12周后观察组平均IOP、昼夜IOP差低于对照组，差异均有统计学意义（P＜0.05）；治疗12周后，观察组PCA和CRA的PSV、EDV高于治疗前，RI低于治疗前，差异均有统计学意义（P＜0.05），且观察组PCA和CRA的PSV、EDV高于对照组，RI低于对照组，差异均有统计学意义（P＜0.05）；治疗12周后，两组患者血浆ET-1和房水TIMP-2较治疗前显著下降，且观察组血浆ET-1和房水TIMP-2含量低于对照组，差异均有统计学意义（P＜0.05）。**结论：**曲伏前列腺素滴眼液治疗POAG患者，能够有效降低患者的眼压、血浆ET-1、房水TIMP-2水平，并改善患者PCA、CRA的血流动力学。

关键词：曲伏前列腺素；原发性开角型青光眼；眼压；血流动力学；ET-1；TIMP-2

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Effects of Travoprost Eye Drops on Intraocular Pressure, Hemodynamics, ET-1 and TIMP-2 in Patients with POAG

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ABSTRACT Objective: To investigate the effects of travoprost eye drops on intraocular pressure, hemodynamics and endothelin-1 (ET-1) and matrix metalloproteinase-2 (TIMP-2) in patients with primary open-angle glaucoma (POAG). **Methods:** A total of 70 patients, who were treated in the 59th Hospital of PLA from February 2015 to February 2017, were randomly divided into control group (n=35) and observation group (n=35). The control group and the observation group were treated with timolol maleate eye drops and travoprost eye drops respectively for 3 months. The average intraocular pressure (IOP) and day and night IOP difference were comparatively analyzed before treatment, 4 weeks, 8 weeks and 12 weeks after treatment. The posterior ciliary artery (PCA), central retinal artery (CRA), peak systolic velocity (PSV), end diastolic velocity (EDV) and vascular resistance index (RI), plasma ET-1 and improve situation of aqueous humor TIMP-2 were compared before treatment and 12 weeks after treatment. **Results:** There were no significant differences in average IOP, day and night IOP difference, hemodynamics of PCA and CRA, plasma ET-1 and aqueous humor TIMP-2 between the two groups before treatment (P>0.05). After 4 weeks, 8 weeks and 12 weeks of treatment, average IOP and day and night IOP difference of the two groups were significantly lower than those before treatment, and average IOP and day and night IOP difference in the observation group were lower than those in the control group after 12 weeks treatment, the differences were statistically significant (P<0.05). After 12 weeks of treatment, the PSV and EDV of PCA and CRA in the observation group were higher than those before treatment, RI was lower than that before treatment, the differences were statistically significant (P<0.05). The PSV and EDV of PCA and CRA in the observation group were higher than those in the control group, RI was lower than that in the control group, the differences were statistically significant (P<0.05). After 12 weeks of treatment, the plasma ET-1 and aqueous humor TIMP-2 in the two groups were significantly lower than those before treatment, and the contents of plasma ET-1 and aqueous humor TIMP-2 in the observation group were lower than those in the control group, the differences were statistically significant (P<0.05). **Conclusion:** Travoprost eye drops can effectively reduce the levels of IOP, plasma ET-1 and aqueous humor TIMP-2 in the treatment of patients with POAG, and improve the hemodynamics of CRA and PCA.

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前言

青光眼是全球第二大致盲疾病，其中原发性开角型青光眼（primary open-angle glaucoma, POAG）是青光眼中最常见的类型，影响全球约 4500 万的患者，且其发病率呈逐年上升趋势[1-3]。POAG 患者治疗的关键手段主要是降眼压（Intraocular pressure, IOP），目前常见的降 IOP 的局部药物有 β- 肾上腺素能拮抗剂、前列腺素类似物、α-2- 肾上腺素能激动剂与胆碱能激动剂等[4-6]；其中前列腺素类似物代表药物曲伏前列腺素降 IOP 效果好，且患者耐受性高，临床上应用曲伏前列腺素治疗 POAG 取得不错的成效[7,8]。高 IOP 是青光眼主要危险因素，其他的危险因素还有眼周血管血流动力差、血浆高水平内皮素 -1（endothelin-1，ET-1）、房水高水平基质金属蛋白酶 -2 抑制因子（matrix metalloproteinase-2, TIMP-2）等，眼周血管血流动力与 ET-1 可通过影响眼周血管收缩，加重视神经缺血，从而影响局部药物代谢。TIMP-2 表达过高可导致细胞外基质合成与降解的动态失衡，影响房水排出，导致 IOP 增高，加重青光眼损害[9-11]。为探讨曲伏前列腺素滴眼液对青光眼患者 IOP、血流动力学及 ET-1、TIMP-2 的影响，旨在为临床治疗 POAG 患者提供参考，我们做了相关研究，具体报道如下。

1 资料与方法

1.1 一般资料

选取 2015 年 2 月至 2017 年 2 月我院眼科收治的 70 例未经过治疗的 POAG 患者作为研究对象，纳入标准：① IOP＞21 mmHg；② IOP 升高时房角开放；③ 青光眼特征性视野缺损；④ 具有青光眼特征性眼底视盘改变；排除标准：① 患有其他能引起视盘改变和视野缺损的眼部疾病患者；② 本次就诊前 1 个月内使用过 β- 受体阻滞剂者，1 周内使用过青光眼治疗的药物者；③ 严重肝肾等重要器官功能障碍者，恶性肿瘤及精神疾病患者；④ 妊娠及哺乳期女性；⑤ 依从性差，不能配合随访和检查的患者。根据随机数字表法将 70 例分为对照组 35 例（70 只眼）和观察组 35 例（70 只眼），其中对照组男 20 例，女 15 例，年龄 36-58 岁，平均年龄（49.92± 2.73）岁，观察组男 18 例，女 17 例，年龄 37-59 岁，平均年龄（49.67± 3.12）岁，两组年龄、性别等一般资料比较无统计学差异（P＞0.05）。本研究经医院伦理委员会审批通过且患者及患者家属均已签署知情同意书。

1.2 药品、试剂及仪器

曲伏前列腺素滴眼液（Alcon Laboratories(UK) Limited，注册证号：H20130813，规格：2.5 mL：0.1 mg）；马来酸噻吗洛尔滴眼液（武汉五景药业有限公司，国药准字 H42021078，规格：5 mL:25 mg）。ET-1 酶联免疫吸附试剂盒购自上海拜力生物科技有限公司生产；TIMP-2 试剂盒购自上海樊克生物科技有限公司；非接触式眼压计购于日本拓普康公司；VOLUSONE10 彩色超声多普勒显像仪购自美国 GE Healthcare 公司。

1.3 治疗方法

对照组患者给予马来酸噻吗洛尔滴眼液滴眼，2 次 /d（早晚各 1 次，1 次 1 滴），观察组患者给予曲伏前列腺素滴眼液滴眼，1 次 /d（睡前 1 次，1 次 1 滴），两组患者治疗周期均为 3 个月。

1.4 观察指标

24 h 测量患者 IOP，测量自早上 7：30 点开始至第二天早上 7:30，每隔两个小时测量一次，22:30~7：00 睡眠时间予床边测 IOP，具体测眼压的时间为 7:30、9:30、11:30、13:30、15:30、17:30、19:30、21:30、23:30、1:30、3:30、5:30 及 7:30。两组治疗前、治疗 4 周后、8 周后、12 周后的平均 IOP、昼夜 IOP 差变化情况；治疗前及治疗 12 周后，受检者取仰卧位，双眼自然闭合，将彩色超声多普勒显像仪探头轻放在眼睑上，检测患者血流动力学，对比两组患者睫状后动脉（Posterior ciliary artery, PCA）和视网膜中央动脉（Central retinal artery, CRA）治疗前后收缩期峰值血流速度（Peak systolic velocity, PSV）、舒张末期血流速度（End diastolic velocity, EDV）及血管阻力指数（Systemic vascular resistance index, RI）等血流动力学指标改善情况；两组患者治疗前和治疗 12 周后清晨间采空腹外周血 5 mL，EDTA 抗凝，颠倒数次充分混匀，室温静置 30 min，3500 r/min 离心 10 min，取血浆；采用酶联免疫吸附测定法(ELISA)检测分析两组患者治疗前、治疗 12 周后分析两组患者治疗前后血浆 ET-1 含量改变情况，并于治疗前和治疗 12 周后抽取房水样本 100-200 μL，采用 ELISA 检测房水中 TIMP-2 的含量。所有操作参考试剂盒说明书进行。

1.5 统计学方法

本研究数据采用 SPSS19.0 软件进行统计学分析处理，计量资料以均数± 标准差（$\bar{x}$± s）表示，实施 t 检验；以 P＜0.05 为差异有统计学意义。

2 结果

2.1 两组患者治疗前后平均 IOP 比较

两组患者治疗前、治疗 4 周后、治疗 8 周后平均 IOP 比较差异无统计学意义（P＞0.05），治疗 4 周、8 周、12 周后，两组患者平均 IOP 较治疗前降低，且治疗 12 周后观察组平均 IOP 低于对照组，差异均有统计学意义（P＜0.05）。详见表 1。

2.2 两组患者治疗前后昼夜 IOP 差比较

两组患者治疗前、治疗 4 周后、治疗 8 周后昼夜 IOP 差比较差异无统计学意义（P＞0.05）；治疗 4 周、8 周、12 周后两组患者昼夜 IOP 差较治疗前明显下降，且治疗 12 周后观察组昼夜 IOP 差明显低于对照组，差异均有统计学意义（P＜0.05）。详见表 2。

2.3 两组患者治疗前后 PCA 血流参数比较

治疗前，两组患者 PCA 血流参数 PSV、EDV 及 RI 比较差异无统计学意义（P＞0.05）；治疗 12 周后对照组 PCA 血流参数与治疗前相比差异无统计学意义（P＞0.05），治疗 12 周后，观察组 PSV、EDV 较治疗前升高，RI 较治疗前降低，且观察组 PSV、EDV 高于对照组，RI 低于对照组，差异均有统计学意义

（P<0.05）。见表 3。

表 1 两组患者治疗前后平均 IOP 比较（$\bar{x}\pm s$）

Table 1 Comparison of average IOP between two groups before and after treatment ($\bar{x}\pm s$, mmHg)

Groups	n	Before treatment	4 weeks after treatment	8 weeks after treatment	12 weeks after treatment
Control group	35	27.12± 2.53	19.98± 2.34*	18.05± 2.24*	17.93± 2.51*
Observation group	35	27.59± 2.35	19.13± 2.41*	17.28± 2.61*	15.38± 2.16*
t		0.184	1.497	1.324	4.556
P		0.901	0.112	0.183	0.001

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

表 2 两组患者治疗前后昼夜 IOP 差比较（$\bar{x}\pm s$）

Table 2 Comparison of day and night IOP difference between two groups before and after treatment ($\bar{x}\pm s$,mmHg)

Groups	n	Before treatment	4 weeks after treatment	8 weeks after treatment	12 weeks after treatment
Control group	35	6.62± 1.78	5.12± 1.13*	4.23± 0.88*	4.19± 0.75*
Observation group	35	6.78± 1.53	4.72± 1.08*	3.92± 0.96*	3.83± 0.66*
t		0.403	0.160	1.408	2.131
P		0.721	0.958	0.126	0.032

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

表 3 两组患者治疗前后 PCA 血流参数比较（$\bar{x}\pm s$）

Table 3 Comparison of PCA blood flow parameters between two groups before and after treatment ($\bar{x}\pm s$)

Groups	n	Time	PSV ($cm\cdot s^{-1}$)	EDV ($cm\cdot s^{-1}$)	RI
Control group	35	Before treatment	9.56± 2.48	2.67± 0.71	0.77± 0.09
		12 weeks after treatment	9.98± 2.34	2.89± 0.63	0.74± 0.11
t			0.728	1.371	1.248
P			0.598	0.162	0.186
Observation group	35	Before treatment	9.59± 1.98	2.73± 0.57	0.76± 0.09
		12 weeks after treatment	14.01± 2.32*	3.86± 0.69*	0.63± 0.08*
t			8.573	7.469	6.386
P			0.001	0.001	0.001

Note: Compared with the control group, *P＜0.05.

2.4 两组患者治疗前后 CRA 血流参数比较

治疗前，两组患者 CRA 血流参数 PSV、EDV 及 RI 比较差异无统计学意义（P＞0.05）；治疗 12 周后对照组 CRA 血流参数与治疗前相比差异无统计学意义（P＞0.05），治疗 12 周后，观察组 PSV、EDV 较治疗前升高，RI 较治疗前降低，且观察组 PSV、EDV 高于对照组，RI 低于对照组，差异均有统计学意义（P<0.05）。详见表 4。

表 4 两组患者治疗前后 CRA 血流参数比较（$\bar{x}\pm s$）

Table 4 Comparison of CRA blood flow parameters between two groups before and after treatment ($\bar{x}\pm s$)

Groups	n	Time	PSV ($cm\cdot s^{-1}$)	EDV ($cm\cdot s^{-1}$)	RI
Control group	35	Before treatment	8.23± 1.42	2.56± 0.61	0.67± 0.08
		12 weeks after treatment	8.97± 1.74	2.78± 0.81	0.64± 0.07
t			1.949	1.283	1.669
P			0.057	0.181	0.102
Observation group	35	Before treatment	8.24± 1.58	2.59± 0.47	0.66± 0.07
		12 weeks after treatment	11.02± 2.01*	3.79± 0.68*	0.60± 0.04*
t			6.433	8.588	4.403
P			0.001	0.001	0.001

Note: Compared with the control group, *P＜0.05.

2.5 两组患者治疗前后血浆 ET-1 和房水 TIMP-2 变化情况

治疗前，两组患者血浆 ET-1 和房水 TIMP-2 比较差异无统计学意义(P＞0.05)；治疗 12 周后两组患者血浆 ET-1 和房水 TIMP-2 均较治疗前降低，且观察组血浆 ET-1 和房水 TIMP-2 低于对照组，差异均有统计学意义(P<0.05)。见表 5。

表 5 两组患者治疗前后血浆 ET-1 和房水 TIMP-2 变化情况($\bar{x}\pm s$)

Table 5 Changes of plasma ET-1 and aqueous humor TIMP-2 between two groups before and after treatment ($\bar{x}\pm s$)

Groups	n	Time	ET-1(ng/L)	TIMP-2(ng/ml)
Control group	35	Before treatment	64.63± 7.89	46.78± 17.03
		12 weeks after treatment	48.92± 7.23	27.21± 3.58
t			8.685	6.653
P			0.001	0.001
Observation group	35	Before treatment	65.27± 8.13	45.321± 5.92
		12 weeks after treatment	44.38± 6.72#	23.85± 3.07#
t			11.695	7.834
P			0.001	0.001

Note: Compared with the control group, #P＜0.05.

3 讨论

青光眼是指 IOP 间断或持续升高的一种眼病，该病起病隐匿，进展迅速、致盲率极高，其中 POAG 约占青光眼患者的 70%[12,13]。POAG 病理机制复杂，眼球内房水产生与流出失衡导致 IOP 持续或间断性增高，造成眼周血管损伤，给眼球内组织和视功能带来不同程度的损害，导致视神经萎缩、视野缩小、视力减退等青光眼特征性改变[14-16]。有效地保护视神经，控制 IOP 在目标值范围内是青光眼治疗的关键。目前临床上较为常用的降 IOP 药物有β- 肾上腺素能拮抗剂和前列腺素类似物两大类，主要作用都是增加房水外流来降低 IOP，前者代表药物是马来酸噻吗洛尔，后者为曲伏前列腺素，马来酸噻吗洛尔作为传统经典的青光眼降 IOP 药物，不少研究表明它可导致较明显的全身不良反应，治疗过程中降 IOP 作用进行性下降，且需早晚两次给药，不利于提高患者依从性[17-19]；而曲伏前列腺素在治疗 POAG 过程中因为具有稳定的降 IOP 作用和良好的患者依从性从而受到国内外临床工作者的广泛认可，曲伏前列腺素是一种合成 F2α 类的前列腺素，滴眼后迅速被角膜酯酶水解为游离酸形式，该游离酸结合并激活睫状肌 FP 前列腺类受体，松弛睫状肌肌肉，引起肌间多种细胞外基质降解，继而经葡萄膜巩膜通路房水外流来降低 IOP[20-22]。

本研究发现，观察组患者治疗 12 周后平均 IOP 和昼夜 IOP 差明显低于对照组患者，差异有统计学意义(P＜0.05)，提示曲伏前列腺素滴眼液降 IOP 的作用强于马来酸塞吗洛尔滴眼液，这与国内外众多学者研究一致[18,22]。观察组 PCA 和 CRA 血流动力学情况较对照组显著改善，差异有统计学意义（P＜0.05），提示曲伏前列腺素滴眼液对眼周血管的血流动力学改善作用较马来酸噻吗洛尔滴眼液更佳。曲伏前列腺素可通过减少眼周血管扩张，延长局部药物作用时间，提高药效，更好地控制患者 IOP 并减少昼夜 IOP 差波动[23-25]；对于 ET-1 和 TIMP-2，本研究发现观察组患者治疗后血浆 ET-1 和房水 TIMP-2 显著低于对照组患者，差异均有统计学意义(P＜0.05)，表明曲伏前列腺素滴眼液降血浆 ET-1 和房水 TIMP-2 效果更好，ET-1 是青光眼发生发展中的危险因素之一，它可以剂量依赖性地增强小梁网的细胞收缩继而增高，ET-1 水平的升高可能在视神经缺血中起重要作用，曲伏前列腺素降低血浆 ET-1 能更好降 IOP 和保护视神经，具体机制目前尚未明确，需要更多研究探索发现[26,27]；TIMP-2 是有效的非活性基质金属蛋白酶非选择性抑制剂，曲伏前列腺素减少房水 TIMP-2 提高房水内基质金属蛋白酶活性，继而引起房水内及肌纤维间细胞外基质组分的降解达到降低 IOP 的目的[28-30]。

综上所述，曲伏前列腺素较马来酸塞吗洛尔能更有效地控制 POAG 患者 IOP 及昼夜 IOP 差，降低血浆 ET-1、房水 TIMP-2 水平，并改善 PCA 和 CRA 血流动力学，值得临床推广。

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