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前列腺素 E1 治疗冠状动脉微血管病变的临床研究 *

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摘要 目的:本研究旨在探索前列腺素 E1(PGE1)对冠状动脉微血管病变(CMVD)治疗的效果及其可能的机制。**方法:**92 例 CMVD 患者随机分为 PGE1 治疗组(47 例)及常规治疗组(45 例)。PGE1 治疗组给予 PGE1 静脉注射,10 μg/次,一日一次。常规治疗组给予等剂量生理盐水静脉注射,一日一次。两组治疗时间均为 10 天。通过治疗前后各组的西雅图心绞痛量表评分、血清血栓调节蛋白(TM)水平、血清超氧化物歧化酶(SOD)水平观察 PGE1 对 CMVD 的治疗效果。**结果:**PGE1 治疗组在西雅图心绞痛量表中的 5 个维度(躯体活动受限程度、心绞痛频率、心绞痛稳定状态、治疗的满意程度、疾病认识)评分均高于常规治疗组(P 均 <0.05)。此外,PGE1 治疗组患者血清 TM 水平较常规治疗组显著下调(PGE1 治疗组 18.25 ± 7.84 vs 常规治疗组 23.1 ± 9.11 , $P < 0.05$),血清 SOD 水平两组间无统计学差异(PGE1 治疗组 78.23 ± 18.61 vs 常规治疗组 71.01 ± 19.1 , $P = 0.07$)。**结论:**PGE1 能够缓解 CMVD 患者的心绞痛状态,提高 CMVD 患者的生活质量,其机制可能与下调血清 TM 水平、保护冠状动脉微血管内皮细胞有关。

关键词:冠状动脉微血管病变;前列腺素 E1;西雅图心绞痛量表;血栓调节蛋白

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Effects of Prostaglandin E1 in Patients with Coronary Microvascular Disease*

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ABSTRACT Objective: In this study, we assessed the effect of prostaglandin E1 (PGE1) in coronary microvascular disease (CMVD) and explored the underlying mechanisms. **Method (s):** 92 patients with CMVD were randomly divided into a PGE1-treatment group ($n=47$, PGE1 10μg/d, iv drip) and a control group ($n=45$, comparable dose of physiological saline). The whole therapeutic course was 10 days. The score of Seattle angina questionnaire(SAQ), the level of thrombomodulin(TM) and superoxide dismutase(SOD) were measured at baseline and after treatment. **Result(s):** PGE1-treatment group improved all SAQ items(physical limitation, angina frequency, angina stability, treatment satisfaction, disease perception) compared with control. Furthermore, the level of TM decreased in PGE1-treatment group compared with control. (PGE1 group: 18.25 ± 7.84 vs control group: 23.1 ± 9.11 , $P < 0.05$). There were no statistical differences between the two groups at the level of SOD (PGE1 group: 78.23 ± 18.61 vs control group: 71.01 ± 19.1 , $P = 0.07$). **Conclusion (s):** PGE1 may play a therapeutic role of CMVD patients in relieving angina and improving the quality of life by decreasing the level of TM and protecting the endothelial cells of coronary microvascular.

Key words: Coronary microvascular disease; Prostaglandin E1; Seattle angina questionnaire; TM

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前言

冠状动脉微血管病变(CMVD)是指因冠状前小动脉(血管内径约为 0.1 mm-0.5 mm)和小动脉(血管内径 < 0.1 mm)的结构和/或功能异常所致的劳力性心绞痛或存在心肌缺血客观证据的临床综合征^[1]。有研究显示,虽然 CMVD 患者冠状动脉造影和/或冠状动脉 CTA 检查未发现阻塞性冠状动脉疾病,但其主要心血管事件及全因死亡率显著高于对照组^[2],因此,临床中应重视对 CMVD 患者的治疗。然而令人遗憾的是,目前临床中尚缺乏治疗 CMVD 患者的特异性药物。前列腺素 E1

(PGE1)具有缓解血管痉挛、抑制血小板聚集、抑制氧化应激等作用,目前在临床中被应用于治疗外周动脉闭塞性疾病^[3-5]。有研究指出,PGE1 可能通过发挥抗炎、改善冠脉血流的作用,减轻不稳定型心绞痛患者冠状动脉支架植入术后的心肌损伤情况^[6],而 PGE1 对于治疗 CMVD 患者的临床证据尚显不足。本研究利用西雅图心绞痛量表(SAQ)观察并评估了 PGE1 治疗 CMVD 的临床效果,并通过比较治疗前后血浆中血栓调节蛋白(TM)、超氧化物歧化酶(SOD)水平的变化,阐明其可能的作用机制。

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1 对象和方法

1.1 一般资料

选择 2016 年 1 月至 2018 年 1 月在我院确诊为 CMVD 的患者 92 例作为研究对象,所有入组患者均符合 CMVD 的诊断

标准^[1]。将以上患者被随机分为 PGE1 治疗组(47 例)及常规治疗组(45 例)。如表 1 所示,两组患者的性别、年龄、身体质量指数(BMI)、高血压史、糖尿病史、血脂异常、吸烟史情况均无统计学差异。

表 1 本研究患者主要一般资料

Table 1 Main clinical characteristics of patients enrolled in the study

variable	PGE1 group (n=47)	Control group (n=45)	P value
Age(yrs)	55.67± 4.04	56.47± 4.15	0.35
Male/Female	16/31	15/30	0.56
BMI(kg/m ²)	27.16± 3.1	26.69± 3.7	0.68
Hypertension	26(55%)	21(47%)	0.51
Diabetes	29(61%)	31(69%)	0.42
Dyslipidemia	36(77%)	32(71%)	0.46
Smoke	9(19%)	11(24%)	0.83

1.2 纳入与排除标准

纳入标准:(1)具有典型的劳力性心绞痛症状;(2)具备以下心肌缺血客观依据中不少于 1 项:静息心电图提示心肌缺血,心电图运动负荷试验阳性(标准为 ST 段下斜型压低或 ST 段抬高 ≥ 0.1 mv,且持续 2 min 以上),核素心肌灌注显像(SPECT)检查显示心肌缺血;(3)冠状动脉造影或冠状动脉 CTA 检查结果正常;(4)左心功能正常。

排除标准:(1)合并其他严重的心脑血管疾病者;(2)近期应用 CYP3A4 抑制剂或使 QT 间期延长的药物者;(3)合并感染性或自身免疫性疾病者;(4)肝、肾功能异常者;(5)因视力、听力或理解力障碍而无法完成西雅图心绞痛量表者。

1.3 研究方法

所有患者根据病情,给予冠心病的二级预防治疗^[7],如阿司匹林、他汀类药物、硝酸酯类药物、 β 受体阻滞剂、ACE 抑制剂。PGE1 组:给予 PGE1 脂微球载体制剂(Lipo-PGE1)(商品名:凯时,生产厂家:北京泰德制药股份有限公司,批准文号:国药准字 H10980023)10 μ g+10 mL 生理盐水/次,一日一次,缓慢静脉注射,持续时间为 10 天。常规治疗组:给予等剂量生理盐水/次,一日一次缓慢静脉注射,持续时间为 10 天。

1.4 观察指标

1.4.1 心绞痛状态及生活质量评估 采用西雅图心绞痛量表(SAQ)^[8]对患者的心绞痛状态及生活质量情况进行评估,包括:躯体活动受限程度、心绞痛频率、心绞痛稳定状态、治疗的满意程度和疾病认识 5 个维度。所有患者在接受治疗前(前 1 天或当天)及结束治疗后 1 天(after treatment)进行量表评估,每个项目满分均为 100 分,分数越高,代表患者心绞痛症状越轻、生活质量越高。

1.4.2 血清血栓调节蛋白(TM)、超氧化物歧化酶(SOD)水平 患者在接受治疗前(前 1 天或当天)及结束治疗后 1 天空腹采静脉血,离心后冻存于 -80 °C 冰箱保存。采用酶联免疫分析法测定血清样本中 TM、SOD 的水平。

1.5 统计学分析

所有数据采用 SPSS 22.0 软件进行统计学数据分析,所有计量资料以(均数 $\pm$ 标准差)表示,采用 t 检验,所有计数资料用百分率表示,采用 χ^2 检验。 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 心绞痛状态及生活质量比较

如表 2 及图 1 所示,在接受治疗后,PGE1 治疗组在西雅图心绞痛量表(SAQ)中的 5 个项目(躯体活动受限程度、心绞痛频率、心绞痛稳定状态、治疗的满意程度、疾病认识)评分均高于常规治疗组,差异有统计学意义($P<0.05$);图 2 所示数据为接受治疗前后患者西雅图心绞痛量表相应评分的差值(difference),PGE1 治疗组亦显著高于常规治疗组,差异有统计学意义($P<0.05$)。以上结果说明,接受 PGE1 治疗后,患者心绞痛症状减轻,生活质量提高。

2.2 血清 TM 水平比较

在接受治疗前,两组患者血清 TM 水平均无统计学差异($P=0.68$)。在接受治疗后,PGE1 治疗组患者血清 TM 水平较常规治疗组显著下调(PGE1 治疗组 18.25 ± 7.84 vs 常规治疗组 23.1 ± 9.11 , $P<0.05$),见图 3。

2.3 血清 SOD 水平比较

在接受治疗前,两组患者血清 TM 水平均无统计学差异($P=0.59$)。在接受治疗后,两组间血清 SOD 水平亦无统计学差异(PGE1 治疗组 78.23 ± 18.61 vs 常规治疗组 71.01 ± 19.1 , $P=0.07$),见图 4。

3 讨论

近年来,冠状动脉微血管病变越来越受到人们的关注,然而由于缺乏大样本人群 CMVD 的流行病学资料及相关的临床试验,目前尚无特异性治疗药物,现有治疗方案与冠心病相似,主要为调整生活方式、抗血小板、他汀类药物、硝酸酯类制剂等

表 2 PGE1 治疗组及常规治疗组患者治疗前后 SAQ 评分

Table 2 SAQ scores at baseline and after treatment of PGE1 group and control group. Data were expressed as $\bar{x} \pm SD$

	Baseline		<i>P</i> value	After treatment		<i>P</i> value
	PGE1 group (n=47)	Control group (n=45)		PGE1 group (n=47)	Control group (n=45)	
physical limitation	62.98± 10.41	63.38± 11.29	0.86	75.55± 12.75	65.91± 9.97	<0.01
anginal stability	30.85± 26.9	31.67± 29.06	0.89	59.04± 26.51	41.87± 21.85	<0.01
anginal frequency	61.06± 20.13	59.78± 19.15	0.76	76.6± 14.18	66.89± 12.97	<0.01
Treatment satisfaction	73.68± 16.62	71.51± 18.71	0.56	84.04± 12.55	76.82± 12.02	<0.01
disease perception	46.66± 16.81	49.69± 14.71	0.37	61.21± 11.21	53.16± 13.77	<0.01

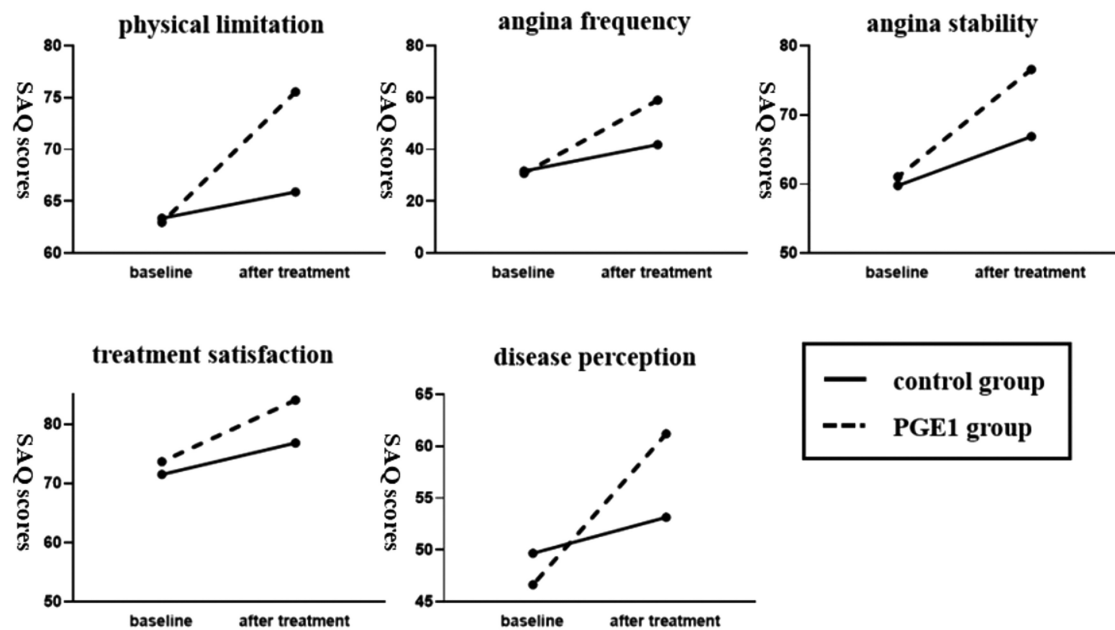


图 1 PGE1 治疗组及常规治疗组患者治疗前后 SAQ 评分(数据为均数)

Fig. 1 Results of the SAQ scale at baseline and follow-up in the PGE1 group and control group. Data were expressed as means

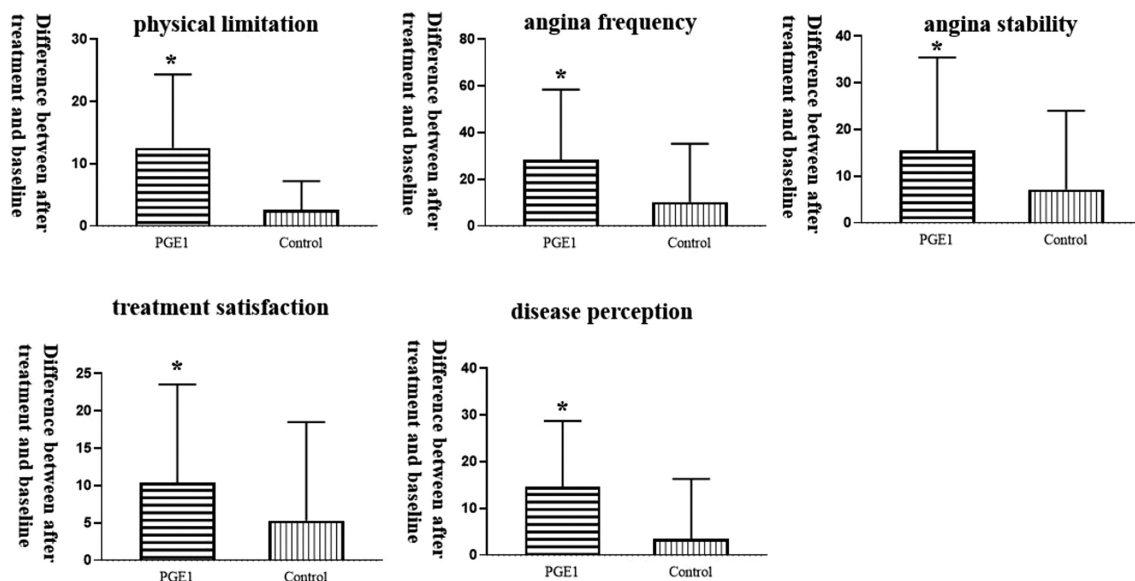


图 2 两组患者治疗前后 SAQ 评分的差值

Fig. 2 Differences of SAQ scores between after treatment and baseline.(* $P < 0.05$ vs baseline)

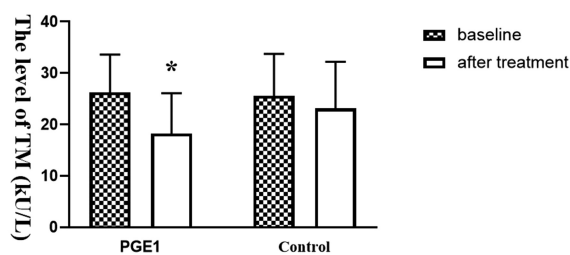


图3 PGE1 治疗组患者治疗后血清 TM 水平显著下调

Fig. 3 The level of TM decreased in PGE1-treatment group compared with control. (PGE1 group: 18.25 ± 7.84 vs control group: 23.1 ± 9.11 , $*P < 0.05$)

治疗^[9-11],近年来,有文献报道雷诺嗉、伊伐布雷定及 ACEI 类药物可能对 CMVD 的治疗有益,但临床证据仍显不足^[12,13]。因此探索改善 CMVD 患者症状的药物具有重要的临床意义和实际应用价值。本研究通过西雅图心绞痛量表,从躯体活动受限程度、心绞痛频率、心绞痛稳定状态、治疗的满意程度和疾病认识 5 个维度,对 PGE1 治疗后 CMVD 患者心绞痛状态及生活质量情况进行了全面评估。研究结果显示,PGE1 治疗能够减轻患者 CMVD 患者活动受限、减少心绞痛发作,同时也增加了患者对于治疗的满意程度和疾病认知。

PGE1 其在人体内分布广泛,具有抑制交感神经、激活腺苷酸环化酶、减少氧自由基的产等生理作用^[14-16]。有报道称,PGE1 具有改善肺血管疾病、糖尿病的微血管病变等作用^[17,18]。Wei LY 等报道^[19],经皮冠状动脉介入治疗(PCI)术前静脉应用 PGE1,可显著改善冠状动脉血流,降低主要心血管事件(MACE)的发生率;Chu-fan L 等研究发现^[20],PGE1 能够减轻 PCI 围术期的心肌损伤。综上,PGE1 可能通过改善内皮细胞功能、抑制氧化应激,从而保护冠状动脉血管内皮及改善血流灌注。值得注意的是,本研究选择的实验药品为 PGE1 脂微球载体制剂(Lipo-PGE1),即将 PGE1 分子封入直径为 $0.2 \mu\text{m}$ 的卵磷脂脂微球中形成的脂肪乳注射液,有效地减少了其在肺循环的灭活,同时增强了其与病变的血管内皮结合的亲和性和靶向性^[21]。

血栓调节蛋白(TM)是由血管内皮细胞合成一种跨膜糖蛋白,在凝血及纤溶过程中均发挥着重要的作用,亦是评价血管内皮损伤的重要标志^[22]。本研究发现,PGE1 治疗后 CMVD 患者血清 TM 较对照组显著下调,表明 PGE1 可能通过改善冠状动脉微血管的内皮细胞功能障碍,发挥缓解心绞痛症状的作用。

超氧化物歧化酶(SOD)是人体内重要的抗氧化应激系统,其可催化活性氧自由基转变为低毒性的 H_2O_2 ,在急性心肌梗死、心肌缺血-再灌注、心力衰竭、心肌炎等多种心脏疾病中均发挥着重要作用^[23,24]。本研究评估了 PGE1 治疗及常规治疗后 CMVD 患者血清 SOD 情况,两组治疗后血清 SOD 水平较治疗前均有不同程度的升高,但两组间比较无统计学差异,我们推测可能有其他氧化应激相关因子参与到 CMVD 的发病过程中,进一步的实验尚待完善。

综上所述,本研究表明 PGE1 能够缓解 CMVD 患者的心绞痛状态,提高 CMVD 患者的生活质量,其机制可能与下调血清 TM 水平、保护冠状动脉微血管内皮细胞有关。

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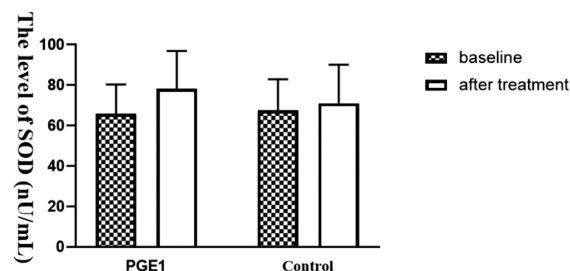


图4 治疗后两组患者血清 SOD 水平无显著差异

Fig. 4 No statistical differences between the PGE1 groups and control at the level of SOD

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