·临床研究·

迈之灵对下肢慢性静脉功能不全患者微循环的改善效果

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【摘 要】 目的 分析迈之灵对下肢慢性静脉功能不全(CVI)患者微循环指标的改善情况。**方法** 入选2016年3月至2017年8月中国医学科学院北京协和医院和赤峰市医院血管外科门诊就诊的CVI患者40例,根据治疗方式分为迈之灵组23例和对照组17例。迈之灵组给予迈之灵及弹力袜治疗,对照组仅采用弹力袜治疗,疗程为4周。观察主要疗效指标[流行病学和经济研究(VEINES)/生活质量(QOL)/症状(Sym)问卷评分、经皮氧分压($TcPO_2$)、皮肤温度]、次要疗效指标(温控血流及阻断后反应性充血)和不良反应,并对疗效和安全性进行评估。采用SPSS 20.0统计软件进行数据处理及分析。组间比较采用t检验、Mann-Whitney U检验或χ^2检验。**结果** 完成病例36例,迈之灵组22例,对照组14例。迈之灵组治疗前相比治疗后VEINES-QOL[(69.3±13.5) *vs* (76.7±11.9)分]、VEINES-Sym[(31.9±7.9) *vs* (36.0±7.4)分]、$TcPO_2$[(45.2±22.3) *vs* (56.3±16.5) mmHg]、皮肤温度[32.6(31.5,33.9)℃ *vs* 31.8(31.0,32.9)℃]和温控血流[(151.4±123.0)% *vs* (418.0±179.5)%]差异均有统计学意义($P<0.05$)。对照组治疗前相比治疗后VEINES-QOL[(64.0±16.1) *vs* (69.0±16.7)分]、VEINES-Sym[(29.3±7.7) *vs* (32.6±7.9)分]和$TcPO_2$[(39.6±16.8) *vs* (51.4±9.9) mmHg]差异有统计学意义($P<0.05$)。迈之灵组相比对照组治疗前后的温控血流差值[(266.6±170.1)% *vs* (−110.1±160.5)%]差异有统计学意义($P<0.05$)。**结论** 迈之灵在一定程度上可改善CVI患者生活质量及临床症状,其疗效可能与其对下肢微循环的改善作用有关。微循环指标中$TcPO_2$、皮肤温度、温控血流可能在一定程度上反映CVI患者下肢微循环的变化。CVI的发病机制可能与下肢微循环改变有密切关联。

【关键词】 下肢静脉功能不全;微循环;迈之灵

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Effects of Aescuven forte on microcirculation for the treatment of chronic venous insufficiency

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【Abstract】 Objective To investigate the effects of Aescuven forte on microcirculation for the treatment of chronic venous insufficiency (CVI). **Methods** A total of 40 outpatients were enrolled in this study from Vascular Surgery Department of Peking Union Hospital and Chifeng Municipal Hospital from March 2016 to August 2017. They were divided into Aescuven forte group ($n=23$) and control group ($n=17$). In a course of 4 weeks, the former were treated with Aescuven forte and pressure (elastic stockings), while the latter only with pressure. Observation focused on the primary efficacy indicators [Venous Insufficiency Epidemiological and Economic Studies-quality of life/symptom score (VEINES-QOL/Sym), transcutaneous oxygen pressure ($TcPO_2$) and skin temperature],

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secondary efficacy indicators [temperature-controlled blood blow and post-occlusion reactive hyperaemia (PORH)] and adverse reactions, and efficacy and safety were evaluated. SPSS statistics 20.0 was used to perform the statistical analysis. Student's *t* test, Mann-Whitney *U* test or Chi-square test was employed for comparison between two groups. **Results** Totally 36 patients (22 in the Aescuven forte group and 14 in the control group) finished the course of the treatment. The readings before *vs.* after treatment in the Aescuven forte group were VEINES-QOL [(69.3±13.5) *vs* (76.7±11.9) scores], VEINES-Sym [(31.9±7.9) *vs* (36.0±7.4) scores], $TcPO_2$ [(45.2±22.3) *vs* (56.3±16.5) mmHg], skin temperature [32.6(31.5,33.9)℃ *vs* 31.8(31.0,32.9)℃] and the temperature-controlled blood flow [(151.4±123.0)% *vs* (418.0±179.5)%], and the differences were statistically significant ($P<0.05$). The readings before *vs.* after treatment in the control group were VEINES-QOL [(64.0±16.1) *vs* (69.0±16.7) scores], VEINES-Sym [(29.3±7.7) *vs* (32.6±7.9) scores], and $TcPO_2$ [(39.6±16.8) *vs* (51.4±9.9) mmHg], and the differences were statistically significant ($P<0.05$). Significant difference was observed in temperature-controlled blood flow between two groups [(266.6±170.1)% *vs* (−110.1±160.5)%, $P<0.05$]. **Conclusion** Our findings indicated that Aescuven forte may improve the quality of life and relieve the symptoms of the patients with CVI, and that a correlation could be established between curative effects and the improved microcirculation. Parameters such as $TcPO_2$, skin temperature, temperature-controlled blood flow may indicate the changes of microcirculation, implying a relation between the pathogenesis of CVI and the alteration of microcirculation.

【Key words】 chronic venous insufficiency; microcirculation; aescuven forte

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下肢慢性静脉功能不全(chronic venous insufficiency, CVI)是因下肢静脉结构和功能异常而导致下肢静脉高压,从而出现一系列临床表现,其发病率高,症状多样,包括下肢肿胀、静脉曲张、皮肤改变和溃疡等[1]。下肢静脉壁及瓣膜原发异常和静脉血栓形成等病变可引起下肢静脉高压,进而增加毛细血管后血管跨壁压,导致皮肤毛细血管损伤、液体渗出、水肿和组织营养不良,使局部组织发生炎症、感染、血栓和组织坏死,最后形成溃疡[2]。

CVI的治疗药物通常以微循环为靶点,目的是减轻症状,改善生活质量[3,4]。迈之灵(Aescuven forte)片是由欧洲马栗树种子提取物制成,主要活性成分是七叶皂苷。既往七叶皂苷对CVI作用的国外研究表明,相比安慰剂,七叶皂苷可明显缓解患者下肢的主观症状并减轻下肢水肿[3],但研究均未涉及微循环指标。为此我们拟联合北京、上海等6家三甲医院血管外科中心,根据统一的研究方案进行前瞻性随机对照研究,旨在研究迈之灵改善CVI患者微循环的可能作用机制。本研究是上述多中心研究的预实验,目前共完成40例,初步探索了迈之灵治疗CVI的微循环相关机制,并筛选药物疗效的相关微循环指标以定量评估CVI患者的病情进展。

1 对象与方法

1.1 研究对象

入选2016年3月至2017年8月在中国医学科学院北京协和医院和赤峰市医院血管外科门诊就诊的CVI患者40例,根据治疗方式分为迈之灵组23例和对照组17例。纳入标准:(1)诊断为CVI(多普勒超声检查提示股总静脉瓣膜返流;股静脉瓣膜关闭时间>0.5 s;穿静脉直径>2.5 mm);(2)年龄18~75岁;(3)签署知情同意书;(4)踝肱指数(ankle brachial index, ABI)>0.85。排除标准:(1)过去6周接受过利尿剂、双氢麦角胺或静脉活性药物治疗;(2)妊娠或哺乳期妇女;(3)存在影响溃疡愈合的因素(使用激素、糖尿病);(4)迈之灵或弹力袜过敏;(5)心源性或肾源性水肿;(6)严重静脉曲张需接受手术治疗;(7)曾接受静脉曲张手术;(8)恶性溃疡。

1.2 方法

迈之灵片铝塑包装,20片/盒,150 mg/片,由德国礼达大药厂提供。弹力袜为浙江绍兴好士德医用品公司生产的治疗型二级中等静脉曲张弹力袜。对照组仅采用弹力袜,迈之灵组除采用弹力袜外,并服用迈之灵片,300 mg,2次/d,共治疗4周,4周后随访。

患者检查前安静休息5 min,检查室安静,避免空气对流,室温恒定25℃,整个检查过程中保持情绪稳定、四肢放松并静止不动。患者平卧位,双下肢与心脏同一水平位。测量经皮氧分压(transcutaneous oxygen pressure, $TcPO_2$)及阻断后反应性充血(post-occlusion reactive hyperaemia, PORH)。检测血压部位位于双下肢小腿中部前外侧,避开静脉、体毛及皮肤破损处。分次阻断双下肢,置下肢专用血

压计,袖带下缘距腘窝上缘 2 cm,阻断 3 min 后迅速排空袖带内气体。

1.3 观察指标

1.3.1 微循环指标评估 微循环检测仪器型号为 PeriFlux5000,是由瑞典 Perimed AB 公司制造的激光多普勒及 $TcPO_2$ 监测系统,该系统可监测健康或患病组织的微循环活性,PSW ExM 软件为该系统的数据采集及分析系统。流行病学和经济研究(Venous Insufficiency Epidemiological and Economic Studies, VEINES)/生活质量(quality of life, QOL)/症状(symptom,Sym)问卷用于评估 CVI 患者生活质量及临床症状,其中 VEINES-QOL 评估患者生活质量,VEINES-Sym 评估临床症状,评分越高提示治疗及恢复效果越佳[5,6]。主要疗效指标包括 VEINES-Sym、VEINES-QOL、$TcPO_2$ 和皮肤温度;次要疗效指标包括温控血流及 PORH 相关微循环指标[7,8]。PORH 相关微循环指标包括静息血流(resting flow,RF)、生物零点(biological zero,BZ)、峰值血流(peak flow,PF)、潜伏时间(time of lurk,TL)、恢复时间(time of recovery,TR)、充血前半衰期(half decrease time between maximum and resting flow before hyperemia,TH1)、达峰时间(time of maximum,TM)、充血后半衰期(half decrease time between maximum and resting flow after hyperemia,TH2)、阻塞面积(areas of occlusion,AO)、充血面积(areas of hyperemia,AH)。

1.3.2 安全性指标 CEAP(clinical, etiological, anatomical, pathophysiological classification)分类法是目前用于规范 CVI 的诊断标准,本研究应用 2004 年修订后的分级方法[9]。主要终点:CEAP 评分减少或增加≥2 分;肢体溃疡愈合、直径扩大>1 cm 或溃疡复发。次要终点:各种原因导致的死亡、主要不良心血管事件、治疗导致的严重不良反应。

1.3.3 不良反应 主要观察治疗后胃肠道的反应、过敏反应、神经系统、心血管系统以及下肢局部不良反应[10]。

1.4 统计学处理

采用 SPSS 20.0 统计软件进行数据处理及分析。计量资料中呈正态分布者采用均数±标准差($\bar{x}\pm s$)表示,呈偏态分布者以中位数(M)和四分位数间距(Q)分别表示数据的集中趋势和离散趋势,2 组比较采用 t 检验和 Mann-Whitney U 检验。计数资料用百分率表示,组间比较采用 χ^2 检验。$P<0.05$ 为差异有统计学意义。

2 结 果

2.1 患者疗程完成情况

入选病例 40 例,36 例完成主要疗效指标观察,迈之灵组 22 例,对照组 14 例,失访 4 例(迈之灵组 1 例,对照组 3 例)。16 例完成次要疗效指标观察,迈之灵组 12 例,对照组 4 例。研究过程中,治疗组及对照组患者均未发生不良反应。

2.2 2 组患者基线资料比较

2 组患者性别、年龄、体质量、血压、病程差异无统计学意义($P>0.05$;表 1)。

2.3 2 组患者主要疗效指标比较

迈之灵组 VEINES-QOL、VEINES-Sym、$TcPO_2$、皮肤温度治疗前后比较差异有统计学意义($P<0.05$);对照组 VEINES-QOL 评分、VEINES-Sym 评分及 $TcPO_2$ 治疗前后比较差异有统计学意义($P<0.05$)。具体见表 2。

2.4 2 组患者次要疗效指标比较

迈之灵组温控血流治疗前后比较差异有统计学意义($P<0.05$);对照组温控血流治疗前后差异无统计学意义($P>0.05$),迈之灵组治疗后温控血流高于对照组患者,差异具有统计学意义($P<0.05$;表 3)。2 组患者其他微循环指标治疗前后比较差异无统计学意义($P>0.05$)。

2.5 2 组患者治疗前后指标差比较

迈之灵组和对照组患者温控血流和皮肤温度治疗前后差值的差异具有统计学意义($P<0.05$;表 4)。

表 1 2 组患者基线资料比较

Table 1 Comparison of baseline data betweeen two groups

Item	Aescuven forte group ($n=22$)	Control group ($n=14$)	t/χ^2	P value
Gender(male/female,n)	12/10	8/6	0	0.9
Age(years, $\bar{x}\pm s$)	58.3±13.9	56.4±12.3	0.4	0.7
Body mass(kg, $\bar{x}\pm s$)	72.3±9.6	70.2±13.7	0.5	0.6
Course of disease[years, $M(Q_1, Q_3)$]	5(1,18)	3(1,7)	-	0.2
SBP(mmHg, $\bar{x}\pm s$)	127.6±13.6	123.4±15.9	0.8	0.4
DBP(mmHg, $\bar{x}\pm s$)	79.5±9.3	77.2±12.1	0.6	0.5

SBP: systolic blood pressure; DBP: diastolic blood pressure. 1 mmHg=0.133 kPa

表2 2组患者主要疗效指标比较

Table 2 Comparison of primary efficacy indices between two groups

Index	Aescuven forte group ($n=22$)		Control group ($n=14$)	
	Before treatment	After treatment	Before treatment	After treatment
VEINES/QOL(score, $\bar{x}\pm s$)	69.3±13.5	76.7±11.9*	64.0±16.1	69.0±16.7*
VEINES/Sym(score, $\bar{x}\pm s$)	31.9±7.9	36.0±7.4*	29.3±7.7	32.6±7.9*
$TcPO_2$(mmHg, $\bar{x}\pm s$)	45.2±22.3	56.3±16.5*	39.6±16.8	51.4±9.9*
Skin temperature[℃, $M(Q_1, Q_3)$]	32.6(31.5,33.9)	31.8(31.0,32.9)*	31.6(27.6,32.8)	32.1(31.2,34.0)

VEINES/QOL: Venous Insufficiency Epidemiological and Economic Studies/quality of life; VEINES/Sym: Venous Insufficiency Epidemiological and Economic Studies/symptom; $TcPO_2$: transcutaneous oxygen pressure. Compared with before treatment, *$P<0.05$. 1 mmHg=0.133 kPa

表3 2组患者次要疗效指标比较

Table 3 Comparison of secondary efficacy indices between two groups

Index	Aescuven forte group ($n=16$)		Control group ($n=4$)	
	Before treatment	After treatment	Before treatment	After treatment
Temperature-controlled blood flow(%, $\bar{x}\pm s$)	151.4±123.0	418.0±179.5*#	294.8±153.7	184.8±22.8
BZ[a](pu, $\bar{x}\pm s$)	7.5±1.8	7.0±2.1	8.7±3.1	6.0±1.0
PF[a][pu, $M(Q_1, Q_3)$]	33(25,37)	33(22,44)	74(22,137)	34(33,35)
RF[a][pu, $M(Q_1, Q_3)$]	20(13,26)	15(9,20)	20(13,142)	18(17,19)
TL(s, $\bar{x}\pm s$)	1.7±2.0	10.1±21.4	0.3±0.6	29.3±12.0
TH1(s, $\bar{x}\pm s$)	10.8±16.7	8.5±10.1	9.7±9.0	27.7±7.6
TM(s, $\bar{x}\pm s$)	42.5±34.0	27.0±26.1	17.7±20.6	61.3±24.8
TH2(s, $\bar{x}\pm s$)	47.8±35.3	32.2±25.7	19.0±22.9	65.0±21.7
TR[s, $M(Q_1, Q_3)$]	3(2,15)	3(2,4)	5(0,17)	19(16,33)
AH(pu·s, $\bar{x}\pm s$)	390.8±446.8	455.2±380.3	65.0±86.1	461.3±145.2
AO[pu·s, $M(Q_1, Q_3)$]	2193(1012,3425)	1586(311,2039)	2079(1111,18 256)	2212(1991,2311)

BZ: biological zero; pu: per unit; PF: peak flow; RF: resting flow; TL: time of lurk; TH1: half decrease time between maximum and resting flow before hyperemia; TM: time of maximum; TH2: half decrease time between maximum and resting flow after hyperemia; TR: time of recovery; AH: areas of hyperemia; AO: areas of occlusion. Compared with before treatment, *$P<0.05$; compared with control group, #$P<0.05$. [a] refer to flow in perfusion units

表4 2组患者治疗前后疗效指标差比较

Table 4 Comparison of efficacy indices differences before and after treatment between two groups

Item	Aescuven forte group ($n=22$)	Control group ($n=14$)
VEINES/QOL(score, $\bar{x}\pm s$)	7.4±5.9	5.0±8.1
VEINES/Sym (score, $\bar{x}\pm s$)	4.1±4.2	3.4±4.4
$TcPO_2$(mmHg, $\bar{x}\pm s$)	11.1±20.2	11.8±17.2
Skin temperature [℃, $M(Q_1, Q_3)$]	−0.6(−1.6, −0.1)*	0.7(−1.0,2.6)
Temperature-controlled blood flow(%, $\bar{x}\pm s$)	266.6±170.1*	−110.1±160.5

VEINES/QOL: Venous Insufficiency Epidemiological and Economic Studies/quality of life; VEINES/Sym: Venous Insufficiency Epidemiological and Economic Studies/symptom; $TcPO_2$: transcutaneous oxygen pressure. Compared with control group, *$P<0.05$. 1 mmHg=0.133 kPa

3 讨 论

CVI病理机制形成的中心因素源于静脉高压，在多种机制的作用下，造成静脉回流功能障碍，使下肢浅静脉、毛细血管及皮肤发生病理改变[1,2]。下肢静脉瓣膜关闭不全、交通静脉瓣膜功能紊乱及肌肉泵功能异常可使病变的静脉瓣再次发生损害[11]。CVI静脉壁结构的改变可能早于瓣膜功能不全，有研究发现静脉曲张继发于静脉壁细胞及细胞外基质破坏，造成静脉骨架结构改变[12]。CVI与炎症反应亦有密切关系，下肢静脉反流可使调节内皮细胞活性的关键因素剪应力减小，从而进一步激发内皮细胞及白细胞的活性，增强黏附分子表达及炎症细胞浸润至静脉壁及瓣叶，形成局部促炎状态[13]。

CVI患者下肢浅表组织不仅毛细血管的分布密度显著降低，毛细血管的形态结构亦显著异常，显微镜下可观察到CVI患者微循环毛细血管存在显著扩张、迂曲，而且毛细血管之间间隔亦显著增大[14,15]。激光多普勒血流量及$TcPO_2$等微循环检测仪器的成熟为研究CVI循环状态提供了可能[16,17]。CVI的病理生理学过程提示潜在的药物治疗方法不仅能够缓解CVI相关临床症状，也可减慢疾病进展[3]。七叶皂苷是欧洲马栗树种子提取物中的主要有效成分，对治疗CVI有显著疗效[18,19]。体外和体内试验都

明确了七叶皂苷可抗水肿、抗炎和提高静脉张力，这主要与其能够促进离子进入通道、提高静脉张力有关[20,21]。

既往研究并无涉及药物对CVI微循环相关指标的作用，目前药物改善微循环的作用机制尚未完全明确，这也是CVI药物研究的不足之处。通过我们的研究发现，迈之灵治疗后与治疗前相比，可显著改善患者的生活质量及临床症状，微循环指标$TcPO_2$、皮肤温度和温控血流均显著改善。2组治疗前后疗效指标差值比较也表明，迈之灵对皮肤温度及温控血流有更显著的改善效果。该预实验提示迈之灵疗效可能与其对下肢微循环的改善作用有关，微循环指标中$TcPO_2$、皮肤温度、温控血流可能在一定程度上反映CVI患者下肢微循环的变化，CVI的发病机制可能与下肢微循环改变有密切关联。随着后续实验的进行，有望进一步验证迈之灵对CVI患者下肢微循环的改善作用，从而筛选出与微循环变化相关联的指标，进一步探索微循环改变在CVI发病机制中的作用。该预实验的主要不足是样本量较小，随着实验的继续进行，该局限可得到一定解决。

实验所用药物为临床使用多年的成熟药物，在国外药物研究实验中的不良反应发生率不超过0.6%，与安慰剂组不良反应发生率间差异无统计学意义。主要的不良反应为胃肠道不适[20]。预期实验可获得CVI微循环改善情况的数据，并初步总结出中国CVI患者的微循环数据库，为下一步CVI的诊疗指南制定及病理生理研究提供理论依据。

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