



温阳化饮养心方对慢性心力衰竭合并利尿剂抵抗患者 中医证候的影响及疗效观察*

吴佳莉¹, 肖丹², 詹洮¹, 袁艺¹, 詹云¹, 刘洪^{2Δ}

1. 宜宾市第二人民医院·四川大学华西医院宜宾医院 中医科/中西医结合科(宜宾 644000);

2. 四川大学华西医院 中西医结合外科医疗单元(成都 610041)

【摘要】目的 本研究通过应用温阳化饮养心方对慢性心力衰竭合并利尿剂抵抗患者进行中医证候研究,并对其进行治疗观察。**方法** 将68例慢性心力衰竭合并利尿剂抵抗的阳气亏虚血瘀证兼痰饮患者随机分为对照组和观察组,对照组在西医基础治疗上予以静脉泵入呋塞米(≥ 80 mg/d),观察组则以低剂量呋塞米(< 80 mg/d)静脉泵入加自拟方温阳化饮养心方(黄芪30 g,茯苓15 g,白术15 g,川芎15 g,淡附片10 g,桂枝10 g,泽泻10 g,知母10 g),以利尿剂抵抗量化指标为主要结局指标,其次比较两组在中医证候、心功能相关指标、终点事件发生率、再入院率之间的差异。**结果** 治疗2周后观察组滤过钠排泄分数(filtration sodium excretion fraction, FENa)为(0.18 \pm 0.04)%,对照组FENa为(0.16 \pm 0.03)%,差异有统计学意义($P=0.037$),观察组24 h尿量、尿Na⁺/K⁺均较治疗前升高,且高于对照组($P<0.05$);两组患者间24 h尿量、尿钠、FENa、尿Na⁺/K⁺治疗变化值的差异均有统计学意义($P<0.05$)。中医证候积分经治疗2周后均有降低,观察组低于对照组($P<0.001$),两组患者间中医证候积分治疗变化值的差异有统计学意义($P<0.001$)。观察组在治疗2周后,心悸、气短、面肢浮肿、自汗、胸闷(痛)、气喘和尿少相对治疗前有改善($P<0.05$),而对对照组仅面肢浮肿、气喘和尿少相对治疗前有改善($P<0.05$)。除外治疗后2周的气喘证候,观察组自汗、胸闷(痛)、气喘(随访24周)和尿少在治疗后不同时间点均优于对照组($P<0.05$)。治疗2周后观察组所测心输出量(cardiac output, CO)、每分钟搏出量(stroke volume, SV)均优于对照组($P<0.05$)。两组患者间N末端脑钠肽前体(N-terminal pro-brain natriuretic peptide, NT-proBNP)、左室射血分数(left ventricular ejection fraction, LVEF)、SV、CO治疗变化值的差异均有统计学意义($P<0.05$)。随访24周后,两组终点事件发生率及再住院率的差异均无统计学意义。**结论** 温阳化饮养心方联合静脉泵入低剂量呋塞米,可改善阳气亏虚血瘀证兼痰饮型慢性心力衰竭合并利尿剂抵抗患者的中医证候,改善患者心功能及利尿剂抵抗,减少利尿剂静脉用量,提高临床疗效,值得临床推广。

【关键词】 温阳化饮养心方 利尿剂抵抗 中医证候 疗效观察

Effects and Efficacy of Wenyang Huayin Yangxin Prescription on the Traditional Chinese Medicine Syndromes of Patients With Chronic Heart Failure Combined With Diuretic Resistance WU Jiali¹, XIAO Dan², ZHAN Tao¹, YUAN Yi¹, ZHAN Yun¹, LIU Hong^{2Δ}. 1. Department of Chinese Medicine/Integrative Medicine, Yibin Second People's Hospital/West China Hospital of Sichuan University Yibin Hospital, Yibin 644000, China; 2. Division of Surgery, Institute of Integrated Traditional Chinese and Western Medicine, West China Hospital, Sichuan University, Chengdu 610041, China
Δ Corresponding author, E-mail: liuhong1980@scu.edu.cn

【Abstract】Objective To study the traditional Chinese medicine (TCM) syndromes of patients with chronic heart failure (CHF) combined with diuretic resistance by using the Wenyang Huayin Yangxin Prescription, and to observe its therapeutic efficacy. **Methods** A total of 68 CHF patients complicated with diuretic resistance and who had Yangqi deficiency and presenting blood stasis syndrome combined with Tanyin were randomly assigned to a control group and an observation group. The control group was given intravenous furosemide (≥ 80 mg/d) via infusion pump in addition to standard Western medical treatment, while the observation group was given intravenous furosemide (< 80 mg/d) via infusion pump along with the Wenyang Huayin Yangxin Prescription (30 g Astragalus, 15 g Poria, 15 g Baizhu, 15 g Chuanxiong, 10 g Danfu tablet, 10 g Cassia, 10 g Alisma, and 10 g Zhimu). The quantitative index of diuretic resistance was used as the primary outcome measure. In addition, the differences between the two groups in TCM syndromes, cardiac function-related indicators, incidence of endpoint events, and readmission rate were compared. **Results** After 2 weeks of treatment, the filtration sodium excretion fraction (FENa) in the observation group was (0.18 \pm 0.04)%, while that of the control group was (0.16 \pm 0.03)%, showing a statistically significant difference ($P = 0.037$). The

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Δ 通信作者, E-mail: liuhong1980@scu.edu.cn

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24-hour urine volume and urine Na^+/K^+ ratio in the observation group increased significantly from baseline levels and were higher than those in the control group ($P < 0.05$). The differences in the changes of 24-hour urine volume, urine sodium, FENa, and urine Na^+/K^+ ratio between the two groups were statistically significant ($P < 0.05$). The TCM syndrome scores decreased in both groups after 2 weeks of treatment, with the observation group showing a significantly greater reduction compared with the control group ($P < 0.001$). The differences in the changes of TCM syndrome scores between the two groups were statistically significant ($P < 0.001$). After 2 weeks of treatment, the observation group showed significant improvements in palpitations, shortness of breath, facial and limb edema, spontaneous sweating, chest tightness (pain), asthma, and oliguria compared with the baseline data ($P < 0.05$), while the control group showed improvements only in facial and limb edema, asthma, and oliguria ($P < 0.05$). Except for the asthma syndrome after 2 weeks of treatment, the observation group showed better outcomes in spontaneous sweating, chest tightness (pain), asthma, and oliguria at various time points after treatment compared with the control group ($P < 0.05$). After 2 weeks of treatment, the observation group had significantly better cardiac output (CO) and stroke volume (SV) compared with those of the control group ($P < 0.05$). The differences in the changes in N-terminal pro-brain natriuretic peptide (NT-proBNP), left ventricular ejection fraction (LVEF), SV, and CO between the two groups were statistically significant ($P < 0.05$). After 24 weeks of follow-up, no significant differences in the incidence of end-point events or readmission rates between the two groups were observed. **Conclusion** The Wenyang Huayin Yangxin Prescription, combined with low-dose intravenous furosemide administered through an infusion pump, can improve the TCM syndromes of patients with Yangqi deficiency and blood stasis syndrome combined with Tanyin in addition to CHF complicated by diuretic resistance. This treatment improves the patients' heart function and diuretic resistance, reduces the intravenous dosage of diuretic, and enhances clinical efficacy. This approach should be more widely applied in clinical settings.

[Key words] Wenyang Huayin Yangxin Prescription Diuretic resistance TCM syndrome Efficacy observation

慢性心力衰竭(chronic heart failure, CHF)是临床上常见危重症之一,发病率及死亡率居高不下,在临床上备受关注,根据China-HF研究结果显示因心力衰竭住院的患者中病死率高达4.1%^[1]。利尿剂作为心力衰竭治疗的最基本药物,能迅速改善液体滞留,在临床上应用广泛,但有研究数据显示约有20%~50%的患者在使用利尿剂治疗CHF时对利尿剂产生抗逆^[2]。与利尿剂治疗反应良好的患者相比,利尿剂抵抗可导致心力衰竭症状恶化,住院时间延长,并可能增加死亡率^[3]。目前利尿剂抵抗量化指标主要有以下3个:滤过钠排泄分数(filtration sodium excretion fraction, FENa) $< 0.2\%$;尿钠 $< 50 \text{ mmol/L}$;尿 $\text{Na}^+/\text{K}^+ < 1.0$ ^[4-6]。指标越低利尿剂抵抗程度越重,因此提升上述指标可视为利尿剂抵抗的改善。中医学早在《素问·水热穴论》中有言“故水病下为跗肿,上为喘呼,不得卧者,标本俱病”,这是中医对心力衰竭导致水肿最早的认识。然而中医并无“利尿剂抵抗”一说,结合其症状、证候以及病因病机,综合历代医家论述^[7],认为本病多以心气虚为本,进一步发展为心阳虚,血瘀贯穿本病始终,血不利则为水,水饮停滞则是最终发展结果。基于中医对心衰疾病发展规律的认识,结合临床证候,从古方中化裁而成自拟方温阳化饮养心汤,临床中常用于治疗CHF且尿少的患者。本研究通过应用温阳化饮养心方对CHF合并利尿剂抵抗患者进行中医证候研究,并观察其疗效,旨

在拓宽临床诊疗思路,发挥中西医协同诊治优势。

1 资料与方法

1.1 研究对象

纳入标准:①年龄不低于40岁,不超过80岁;②符合西医诊断标准且中医辨证符合阳气亏虚血瘀证兼痰饮;③NYHA心功能分级为Ⅲ~Ⅳ级,经标准化治疗并且口服呋塞米80 mg/d(或托拉塞米40 mg/d)后仍出现利尿剂抵抗者;④已签署知情同意书者。排除标准:①存在严重心血管不良事件,如急性冠状动脉综合征、恶性心律失常、休克等;②合并重度瓣膜狭窄或反流、梗阻性肥厚型心肌病、难以纠正的重度肺高压;③存在严重肝功能不全、重症感染者;④使用辅助循环装置、机械通气的患者;⑤对本研究中的药物过敏者;⑥无自主行为能力配合本研究持续随访观察者。筛选2020年10月-2024年1月符合入组条件的68例患者,均来自宜宾市第二人民医院住院患者,采用简单随机数字分组法将其均分为观察组和对照组。本研究经宜宾市第二人民医院医学伦理委员会批准(编号:2021-006-01)。

样本量计算:根据前期临床资料,单纯西医治疗的患者治疗后的FENa平均值为 $(0.16 \pm 0.03)\%$,预期在常规西药治疗的基础上使用中药汤剂治疗后FENa能提高20%。利用成组设计 t 检验样本量计算公式:

$$N = \frac{4(t_{\alpha/2} + t_{\beta})^2 S^2}{\delta^2}$$

计算得到每组样本量至少需要22例,控制失访率为20%,则每组至少纳入27例。

1.2 诊断标准参考依据

1.2.1 西医诊断标准

参照《中国心力衰竭诊断和治疗指南(2018)》^[8]进行诊断,并符合Framingham的心功能分级标准。利尿剂抵抗的临床判断则以每日应用呋塞米剂量 ≥ 80 mg或同等剂量利尿剂下尿量仍 $< 0.5 \sim 1.0$ mL/(kg·h),且FENa $< 0.2\%$;尿钠 < 50 mmol/L;尿Na⁺/K⁺ < 1.0 为标准^[9]。

1.2.2 中医辨证

符合《慢性心力衰竭中西医结合诊疗专家共识(2016)》^[10]中阳气亏虚血瘀证兼痰饮证型的诊断标准。

1.3 治疗方式

两组入院后均参照《中国心力衰竭诊断和治疗指南(2018)》^[8]进行治疗,在其他心力衰竭治疗措施不变的情况下,对照组采用静脉持续微量泵泵入呋塞米(≥ 80 mg/d),如需抗血小板治疗则使用替格瑞洛或氯吡格雷代替阿司匹林。观察组则采用低剂量呋塞米(< 80 mg/d)持续静脉泵入基础上加用温阳化饮养心方(黄芪30 g,茯苓15 g,白术15 g,川芎15 g,淡附片10 g,桂枝10 g,泽泻10 g,知母10 g),采用统一标准免煎颗粒,每日一剂。两组观察治疗疗程均为2周。

1.4 主要观察指标

主要观察指标为利尿剂抵抗评价指标。采集患者治疗前后24 h尿量,测定尿钠、尿钾、尿肌酐及静脉抽血测定血钠、血肌酐水平,根据[(尿钠 \times 血肌酐)/(血钠 \times 尿肌酐)] $\times 100\%$ 计算FENa。24 h尿量越多,尿钠、FENa以及尿Na⁺/K⁺升高提示利尿剂抵抗有所改善。

1.5 次要观察指标

1.5.1 中医证候积分

依据2002版《中药新药临床研究指导原则》中对心力衰竭中医证候的表述制定量表,共15项内容,每项按不同程度分为无(0分)、轻(1分)、中(2分)、重(3分),总分45分,积分越高表示患者的中医证候越重^[11]。在治疗前及治疗2周后进行评分,积分下降表示中医证候有所改善。随访24周对主要中医证候“心悸”“气短”“疲倦乏力”“面肢浮肿”“自汗”“胸闷(痛)”“气喘”“尿少”进行评分,观察以上8个中医证候的变化情况。

1.5.2 心功能评价指标

治疗前后采集静脉血测定血清中N末端脑钠肽前体(N-terminal pro-brain natriuretic peptide, NT-proBNP)水

平,测值越高,心力衰竭程度越重。通过心脏彩超检测治疗前后患者的左室射血分数(left ventricular ejection fraction, LVEF)、心输出量(cardiac output, CO)以及每分钟搏出量(stroke volume, SV),测值越小表示心功能越差。

1.5.3 终点事件及再住院率

随访24周,对所有入组患者进行终点事件发生率及再住院率的统计。以发生不良心血管事件及全因死亡为终点事件。其中不良心血管事件包括纳入时未发生但在随访过程中发生的各种心脏疾病;全因死亡是指在随访过程中出现的任何原因的死亡事件。再住院率是指在随访周期内因心力衰竭复发加重再次入院的患者比例。

1.6 统计学方法

采用SPSS22.0用于统计描述及推断,定性资料采用频数及百分比表示,定量资料采用 $\bar{x} \pm s$ 或中位数及四分位数表示。对于观察组与对照组的比较分析,定性资料采用卡方检验;定量资料符合正态分布时,采用两独立样本t检验,不符合正态分布时,采用秩和检验。对于重复测量资料,采用重复测量方差分析,两两比较采用Bonferroni法。 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 患者基线资料比较

观察组包括18例男性,16例女性;平均年龄(77.47 \pm 5.89)岁;病史(6.59 \pm 1.62)年;NYHA心功能分级Ⅲ级患者19例,Ⅳ级患者15例;基础心脏疾病包含17例冠心病,8例高血压心脏病,2例扩张型心肌病,4例风湿性心脏瓣膜病,3例肺源性心脏病。对照组包括19例男性,15例女性;平均年龄(76.62 \pm 6.21)岁;病史(6.35 \pm 1.87)年;NYHA心功能分级Ⅲ级患者18例,Ⅳ级患者16例;基础心脏疾病包含15例冠心病,9例高血压心脏病,3例扩张型心肌病,3例风湿性心脏瓣膜病,4例肺源性心脏病。基线资料可比($P > 0.05$),见表1。

2.2 治疗前后两组患者利尿剂抵抗量化指标的比较

各指标治疗前组间差异均无统计学意义。治疗2周后观察组患者24 h尿量、FENa、尿Na⁺/K⁺均较治疗前升高,且高于对照组,差异有统计学意义($P < 0.05$)。两组患者间24 h尿量、尿钠、FENa、尿Na⁺/K⁺治疗变化值的差异均有统计学意义($P < 0.05$),观察组上述各指标的治疗变化值大于对照组。见表2。

2.3 中医证候的影响

两组患者的中医证候积分在基线一致的情况下($P > 0.05$),经治疗2周后均有降低,且治疗后观察组中医

表1 患者一般情况(基线资料)比较

Table 1 Comparison of patients' general condition (baseline data)

Item	Observation group (n=34)	Control group (n=34)	χ^2/t	P
Age/yr., $\bar{x} \pm s$	77.47±5.89	76.62±6.21	0.89	0.38
Male/case (%)	18 (52.94)	19 (55.88)	0.59	1.00
Medical history/years, $\bar{x} \pm s$	6.59±1.62	6.35±1.87	0.59	0.56
NYHA classification/case (%)			0.06	1.00
III	19 (55.88)	18 (52.94)		
IV	15 (44.12)	16 (47.06)		
Etiological composition/case (%)			0.67	0.96
Coronary heart disease	17 (50.00)	15 (44.12)		
Hypertensive cardiovascular disease	8 (23.53)	9 (26.47)		
Dilated cardiomyopathy	2 (5.88)	3 (8.82)		
Rheumatic heart disease	4 (11.76)	3 (8.82)		
Pulmonary heart disease	3 (8.82)	4 (11.76)		

表2 治疗前后两组患者利尿剂抵抗量化指标比较

Table 2 Comparison of quantitative indicators of diuretic resistance between the two groups before and after treatment

Group	Urine volume in 24 hours/(L/d)			Urine sodium/(mmol/L)			FENa/%			Urine Na ⁺ /K ⁺		
	Prior to treatment	After 2-week treatment	Change in value	Prior to treatment	After 2-week treatment	Change in value	Prior to treatment	After 2-week treatment	Change in value	Prior to treatment	After 2-week treatment	Change in value
Observation (n=34)	445.59±64.77	1335.29±363.60	889.71±321.1	34.26±6.89	47.21±6.00	12.00 (8.00, 17.00)	0.15±0.03	0.18±0.04	0.03 (0.03, 0.05)	0.30 (0.20, 0.60)	1.10 (0.88, 1.30)	0.65 (0.50, 0.83)
Control (n=34)	434.41±71.87	1145.59±248.91	711.18±186.17	36.21±5.44	44.18±7.32	9.00 (4.00, 10.25)	0.14±0.03	0.16±0.03	0.02 (0.01, 0.03)	0.35 (0.20, 0.50)	0.80 (0.70, 1.10)	0.50 (0.40, 0.70)
<i>t</i>	0.674	2.510	2.805	-1.289	1.866	3.473	0.488	2.132	4.098	0.751	2.441	2.209
<i>P</i>	0.503	0.015	0.007	0.202	0.067	0.001	0.627	0.037	<0.001	0.453	0.015	0.027

FENa: filtration sodium excretion fraction. * Median (P_{25} , P_{75}).

证候积分低于对照组($P < 0.001$); 两组患者间中医证候积分治疗变化值的差异有统计学意义($P < 0.001$), 观察组中医证候积分变化值大于对照组。见表3。

表3 治疗前后两组患者中医证候积分比较

Table 3 Comparison of TCM syndrome scores between the two groups before and after treatment

Group	<i>n</i>	Prior to treatment	After 2-week treatment	Change in value
Observation	34	38.68±1.93	16.26±3.50	22.41±2.50
Control	34	38.76±1.99	22.91±3.37	15.85±2.19
<i>t</i>		-0.186	-7.976	11.507
<i>P</i>		0.853	<0.001	<0.001

对于心悸、气短、疲倦乏力和面肢浮肿等证候指标, 无论是观察组还是对照组, 随着治疗时间的延长, 评分均逐渐下降($P < 0.05$); 两两比较发现, 观察组在治疗2周后, 心悸、气短和面肢浮肿相对治疗前有改善($P < 0.05$), 而对照组仅面肢浮肿相对治疗前有改善($P < 0.05$); 随访24周后, 两组上述指标均较治疗前有改善($P < 0.05$)。组间比

较发现, 无论是治疗2周后还是随访24周, 上述指标的组间差异均无统计学意义。

对于自汗、胸闷(痛)、气喘和尿少的证候指标, 无论是观察组还是对照组, 随着治疗时间的延长, 评分均逐渐下降($P < 0.01$); 两两比较发现, 观察组在治疗2周后, 自汗、胸闷(痛)、气喘和尿少相对治疗前有改善($P < 0.05$), 而对照组仅气喘和尿少相对治疗前有改善($P < 0.05$); 随访24周后, 两组上述指标均较治疗前有改善($P < 0.05$)。组间比较发现, 除外治疗后2周的气喘证候, 其余上述指标在治疗2周后和随访24周的组间差异均有统计学意义($P < 0.05$), 观察组更优。见表4。

2.4 治疗前后两组患者的心功能指标变化情况

治疗前基线一致($P > 0.05$); 治疗2周后观察组所测CO、SV均有升高, 优于对照组($P < 0.05$)。两组患者间NT-proBNP、LVEF、SV、CO治疗变化值的差异均有统计学意义($P < 0.05$), 观察组NT-proBNP、LVEF、SV、CO指标的治疗变化值大于对照组。见表5。

表 4 不同中医证候变化比较

Table 4 Comparison of changes in different TCM syndromes (points)

TCM syndrome	Observation group (n=34)			Control group (n=34)		
	Prior to treatment	After 2-week treatment	Follow-up 24 weeks	Prior to treatment	After 2-week treatment	Follow up 24 weeks
Palpitations	2.79±0.41	2.41±0.70 [*]	1.58±0.95 [*]	2.76±0.43	2.65±0.54	2.00±0.78 [*]
F		46.644			23.516	
P		<0.001			<0.001	
Shortness of breath	2.32±0.47	2.06±0.60 [*]	1.76±0.70 [*]	2.38±0.49	2.25±0.61	2.08±0.67 [*]
F		16.368			4.595	
P		<0.001			0.014	
Weariness	2.85±0.36	2.73±0.45	2.44±0.61 [*]	2.79±0.41	2.68±0.53	2.53±0.51 [*]
F		12.706			5.674	
P		<0.001			0.005	
Edema of the face and limbs	2.88±0.33	2.44±0.61 [*]	2.24±0.55 [*]	2.85±0.36	2.58±0.50 [*]	2.47±0.56 [*]
F		29.76			10.500	
P		<0.001			<0.001	
Spontaneous sweating	2.91±0.29	2.18±0.52 ^{*,Δ}	2.03±0.67 ^{*,Δ}	2.88±0.33	2.74±0.45	2.73±0.46 [*]
F		79.395			8.414	
P		<0.001			<0.001	
Chest tightness (pain)	2.76±0.43	2.06±0.60 ^{*,Δ}	1.82±0.72 ^{*,Δ}	2.82±0.39	2.68±0.53	2.41±0.70 [*]
F		51.058			5.232	
P		<0.001			0.008	
Asthma	2.82±0.39	2.32±0.39 [*]	1.85±0.61 ^{*,Δ}	2.85±0.36	2.56±0.50 [*]	2.47±0.56 [*]
F		54.019			10.560	
P		<0.001			<0.001	
Oliguria	2.79±0.41	2.12±0.60 ^{*,Δ}	1.76±0.74 ^{*,Δ}	2.82±0.39	2.47±0.51 [*]	2.26±0.67 [*]
F		68.083			19.574	
P		<0.001			<0.001	

* $P < 0.05$, vs. prior to treatment in the same group; Δ $P < 0.05$, vs. control group at the same time point.

表 5 治疗前后两组患者心功能指标变化情况

Table 5 Changes of cardiac function indexes in two groups before and after treatment

Group	NT-proBNP/(pg/mL)			LVEF/%			SV/mL			CO/(L/min)		
	Prior to treatment	After 2-week treatment	Change in value	Prior to treatment	After 2-week treatment	Change in value	Prior to treatment	After 2-week treatment	Change in value	Prior to treatment	After 2-week treatment	Change in value
Observation (n=34)	27793.38±6424.44	4552.74±4087.34	23240.65±4220.49	34.53±6.95	39.44±7.99	5.00(4.00, 6.00)	32.97±6.05	58.82±7.96	25.85±3.98	3.32±0.21	3.94±0.36	0.60(0.40, 0.83)
Control (n=34)	26387.53±6284.01	6588.71±4433.79	19798.82±3890.10	34.09±6.81	36.00±6.82	2.00(1.00, 2.25)	31.88±4.93	54.50±8.77	22.62±4.91	3.27±0.20	3.73±0.28	0.50(0.20, 0.60)
t/Z	0.912	-1.969	3.496	0.265	1.910	6.004	0.813	2.127	2.985	1.132	2.727	1.991
P	0.365	0.053	0.001	0.792	0.060	<0.001	0.419	0.037	0.004	0.262	0.008	0.046

NT-proBNP: N-terminal pro-brain natriuretic peptide; LVEF: left ventricular ejection fraction; SV: stroke volume; CO: cardiac output. * Median (P_{25} , P_{75}).

2.5 两组患者终点事件发生率及再住院率比较

随访24周后, 两组终点事件发生率及再住院率差异均无统计学意义。见表6。

3 讨论

利尿剂抵抗目前尚无统一定义, 根据《心力衰竭患者利尿剂抵抗诊断及治疗中国专家共识2024》, 将利尿剂抵抗暂时定义为在充分使用利尿剂的情况下, 即使增加利

表 6 两组患者终点事件发生率及再住院率比较

Table 6 Comparison of end-point event rate and readmission rate between the two groups

Group	n	Incidence of endpoint events/case (%)	Readmission rate/case (%)
Observation	34	3 (8.82)	6 (17.65)
Control	34	6 (17.65)	10 (29.41)
χ^2		1.15	1.31
P		0.48	0.39

利尿剂剂量充血状态仍然持续存在,利钠及利尿反应仍降低或消失^[12]。

目前研究认为心力衰竭患者利尿剂抵抗的发病机制主要包括远曲小管细胞结构破坏、利尿剂药代动力学改变、药物相互作用所致药效动力学改变以及肾素-血管紧张素-醛固酮系统(RAAS)被激活有关^[13]。持续的袢利尿剂使用会导致远端肾小管细胞肥大以及功能亢进而影响利钠反应^[14-15]。此外,CHF患者体内循环有机酸水平的升高会引起利尿剂的药代动力学改变,降低利尿剂的利用率^[16]。另有研究显示阿司匹林类非甾体抗炎药可抑制钠和水的排泄,减弱利尿效果^[17],因此本研究中抗血小板治疗避免使用了阿司匹林。RAAS激活最终导致钠重吸收增加,促使“利尿后钠潴留”和“利尿剂制动”现象的发生,进而促进利尿剂抵抗的发展^[18]。基于上述发病机制,临床通过增加利尿剂剂量、更换利尿剂及用法、联合用药、使用可增加肾血流的药物以及超滤等方法改善利尿剂抵抗^[19-23],虽有一定效果,但存在明显不良反应且易复发^[24]。

近年来不少医家提出发挥中西医联合治疗优势,协同攻克难治性心力衰竭。中医学认为CHF患者心脏功能失调,心失所养而引起痰浊、水饮等停滞于体内,故而阳气虚弱致水湿停滞为主要病机^[25]。《景岳全书·肿胀》曰:“水肿证以精血皆化为水,……治宜温补脾肾,此正法也”。《金匱要略·水气病脉证并治》有云:“……诸有水者,腰以下肿,当利小便”。《素问》中提出了“……平治于权衡,去菀陈莖……”的活血化瘀理念。上述中医经典理论均奠定了心水病当以“温阳益气,活血利水”为主的基本治疗法则。本研究因循此则,将自拟方温阳化饮养心汤用于治疗CHF利尿剂抵抗(阳气亏虚血瘀证兼痰饮)患者。

本方中黄芪为君,补益肺脾,助心行血,治气虚不运,水湿停聚之浮肿尿少,在治疗中发挥补气利水消肿之效。黄芪中的有效成分主要包含黄芪苷、黄芪多糖和黄酮类等,其中黄酮类成分具有利尿作用,靶点主要涉及TNF信号通路、HIF-1、PI3K-Akt信号通路、FoxO信号通路、p53信号通路等^[26],研究显示采用黄芪甲苷进行预处理可显著降低心肌细胞中的蛋白质含量,减少心钠素和脑钠素mRNA的表达,增加ATP/AMP,并降低游离脂肪酸的含量,预防心功能障碍^[27]。由此推测,黄芪可能通过降低有机酸水平,改变了利尿剂药代动力学,通过多靶点信号通路,提高利尿剂的利用率,改善利尿剂抵抗。本方中附子、茯苓、泽泻、白术、桂枝配伍,由经方“五苓散”及“真武汤”化裁而来,以利水除湿、温阳化气为主要作用。其中,泽泻、茯苓具有利水除湿的功效,而白术运化

水湿之外兼补脾气,与茯苓相结合,既有补益之效,又有助“津液四布”之功。其中附子、桂枝相需为用,共奏温阳化气利水之效。现代研究表明,五苓散通过下调白细胞介素(interleukin, IL)-32水平,抑制炎症因子的释放减轻炎症损伤,从而调节糖脂代谢,修复心肌损伤^[28]。进一步研究显示,五苓散可有效改善血管微循环及肾脏功能,具有降低蛋白尿、改善血管通透性、下调炎症因子等抗炎利尿作用^[29]。多项临床研究显示,真武汤可显著缓解CHF患者的心悸、胸闷气短、水肿等症候,降低IL-6、肿瘤坏死因子 α 、超敏C反应蛋白、超氧化物歧化酶、一氧化氮等炎症指标,改善LVEF、左室舒张末期与收缩末期内径、6 min步行实验、脑尿钠肽、NT-proBNP等相关实验室指标,究其原因,可能与其改善了基质金属蛋白酶以及基质金属蛋白酶抑制剂的沉积或过度降解有关,减轻心肌纤维化程度,抑制RAAS系统,维持心肌结构的稳定性,促进水钠排泄,改善利尿剂抵抗^[30-33]。另有学者基于网络药理学和分子对接技术对真武汤治疗CHF可能的机制进行预测,通过实验验证真武汤能够显著改善CHF模型大鼠心功能的相关指标,提高心肌组织AKT1、PPARG mRNA与蛋白表达水平,同时降低CASP3 mRNA与蛋白的表达,通过AKT1、IL-6、TNF、PPAGR、CASP3等靶点,阻断RAAS系统激活,改善利钠反应,发挥治疗CHF的作用^[34]。川芎有活血化瘀、行气止痛之效,川芎中的化学成分(苯酞类化合物、生物碱类及有机酸等)具有抗炎、抗氧化、保护心肌和防止细胞凋亡等功效^[35]。知母虽甘寒,在本方中有“阳中求阴”之意,避免阳盛燥生,且动物实验证实知母中所含的知母皂苷B II可通过PI3K/Akt通路,阻止过氧化氢诱导的H9c2心肌细胞损伤,起到保护心肌细胞的作用^[36]。川芎、知母虽无直接改善利尿剂抵抗的功效,但在组方中与其他药物协同发挥保护心肌细胞的作用,推测在改善心力衰竭症状的同时可减轻患者的利尿剂抵抗。本研究使用温阳化饮养心方联合持续静脉微量泵泵入低剂量呋塞米方案,与对照组相比更能改善CHF合并利尿剂抵抗患者的中医证候,既减少利尿剂静脉用量,又改善患者心功能,提升利尿剂抵抗量化指标。但目前尚未完全明确温阳化饮养心方的作用机制,有待后续研究证实。

本研究存在一定局限性,仅选取了一家医院的数据进行分析,发生利尿剂抵抗的患者相对偏少,随访时间尚短,可能会造成偏倚,亦不排除存在地域偏差。为有效预防CHF患者利尿剂抵抗的发生和改善患者预后提供理论依据,仍需继续扩充样本量,开展多中心、跨区域、前瞻性的深入研究。

* * *

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