

doi: 10.13241/j.cnki.pmb.2023.16.016

补阳还五汤联合西药治疗小儿过敏性紫癜性肾炎的疗效 及对机体血管内皮功能的影响研究*

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摘要 目的:探讨补阳还五汤联合西药治疗小儿过敏性紫癜性肾炎的疗效及对机体血管内皮功能的影响。**方法:**选取我院 2019 年 1 月到 2022 年 12 月收治的 86 例过敏性紫癜性肾炎患儿作为研究对象,分为观察组与对照组,每组 43 例。对照组患儿采取常规西药治疗,观察组患儿采取补阳还五汤联合西药常规治疗,对比两组患儿临床疗效,并对比治疗前与治疗 3 个月后患儿的肾功能变化、炎症因子水平变化、血管内皮功能与凝血功能变化。**结果:**观察组治疗总有效率较对照组高($P<0.05$);两组患儿治疗前明胶酶相关脂质运载蛋白(NGAL)、血肌酐(SCR)、血尿素氮(BUN)对比无差异($P>0.05$),治疗后两组患儿 NGAL、SCR、BUN 水平均升高,观察组较对照组高($P<0.05$);两组患儿治疗前转化生长因子- $\beta 1$ (TGF- $\beta 1$)、白细胞介素-18(IL-18)和白细胞介素-6(IL-6)相关炎症因子水平对比无差异($P>0.05$),治疗后观察组患儿 TGF- $\beta 1$ 、IL-18 和 IL-6 相关炎症因子水平低于对照组($P<0.05$);两组患儿治疗前 D-二聚体、纤维蛋白原(FIB)、一氧化氮(NO)和内皮素-1(ET-1)水平对比无差异($P>0.05$),治疗后观察组患儿 D-二聚体、FIB 和 ET-1 水平均降低,且观察组低于对照组,NO 水平升高,观察组较对照组高($P<0.05$)。**结论:**补阳还五汤联合西药治疗小儿过敏性紫癜性肾炎临床疗效显著,能够改善患儿肾功能,降低机体炎症反应,提升凝血功能的同时,进一步改善患儿血管内皮功能,值得临床应用推广。

关键词:补阳还五汤;过敏性紫癜性肾炎;血管内皮功能;肾功能;凝血功能;炎症因子

中图分类号:R692.34 文献标识码:A 文章编号:1673-6273(2023)16-3083-05

Effect of Buyang Huanwu Decoction and Western Medicine on Allergic Purpura Nephritis in Children and Its Effect on Vascular Endothelial Function*

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ABSTRACT Objective: To investigate the therapeutic effect of Buyang Huanwu Decoction (BHD) combined with western medicine on children with allergic purpura nephritis (HSPN) and its effect on vascular endothelial function. **Methods:** 86 children with Henoch Schonlein purpura nephritis admitted to our hospital from January 2019 to December 2022 were selected as the research objects, and they were divided into the observation group and the matched group, with 43 cases in each group. The children in the matched group were treated with conventional western medicine, and the children in the observation group were treated with Buyang Huanwu Decoction combined with conventional western medicine. The clinical effects of the two groups of children were compared, and the changes in renal function, inflammatory factor levels, vascular endothelial function and blood coagulation function before and after treatment for 3 months were compared. **Results:** The total effective rate of the observation group was higher than that of the matched group ($P<0.05$); Before treatment, there was no difference between the two groups in the levels of gelatinase related lipid carrier protein (NGAL), serum creatinine (SCR) and blood urea nitrogen (BUN) ($P>0.05$). After treatment, the levels of NGAL, SCR and BUN in the two groups were higher than those in the matched group ($P<0.05$); There was no difference in the levels of transforming growth factor- $\beta 1$ (TGF- $\beta 1$), interleukin-18 (IL-18) and IL-6 between the two groups ($P>0.05$). The levels of TGF- $\beta 1$, IL-18 and IL-6 related inflammatory factors in the post-treatment observation group were lower than those in the matched group ($P<0.05$); There was no difference in the levels of D-dimer, fibrinogen (FIB), nitric oxide (NO) and endothelin-1 (ET-1) between the two groups before treatment ($P>0.05$). After treatment, the levels of D-dimer, FIB and ET-1 in the observation group were lower than those in the matched group, and the level of NO in the observation group was higher than that in the matched group ($P<0.05$). **Conclusion:** Buyang Huanwu Decoction combined with western

* 基金项目:陕西省名中医罗世杰工作室项目(陕卫中医发[2018]95 号)

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(收稿日期:2023-01-12 接受日期:2023-02-08)

medicine has a significant clinical effect on children with Henoch Schonlein purpura nephritis. It can improve the renal function of children, reduce the inflammatory reaction of the body, enhance the blood coagulation function, and further improve the vascular endothelial function of children. It is worthy of clinical application and promotion.

Key words: Buyang Huanwu Decoction; Henoch Schonlein purpura nephritis; Vascular endothelial function; Renal function; Coagulation function; Inflammatory factor

Chinese Library Classification(CLC): R692.34 **Document code:** A

Article ID: 1673-6273(2023)16-3083-05

前言

过敏性紫癜(Henoch-Schonlein purpura, HSP)属于全身性系统血管炎疾病的一种,多发生于儿童群体。而紫癜性肾炎(Henoch-Schonlein purpura nephritis, HSPN)主要指过敏性紫癜发生6个月内继发的肾炎,发病率约为所有过敏性紫癜患儿的15%-62%,仅次于儿童肾病综合征^[1]。HSPN患儿的肾脏病理组织学改变多为肾小球系膜细胞的基质增生与增殖,出现蛋白尿现象。研究发现^[2],HSPN经过积极治疗后,患儿预后情况较好,但是依然有1%-15%的患儿依然会出现进行性肾损害现象。虽然过敏性紫癜肾炎当前并无统一治疗方案,但随着临床上对过敏性紫癜研究加深,越来越多学者认为炎症反应和免疫系统失常是该病发生的重要机制^[3]。当前临床上对于过敏性紫癜多采取血浆置换、血管紧张素受体拮抗剂、血管紧张素转换酶抑制剂、免疫抑制剂、抗凝以及糖皮质激素等药物对症治疗^[4,5]。但临床实践发现,虽然常规西药治疗对于过HSPN具有一定疗效,但部分患儿疾病控制效果不佳,且不良反应较多,因此还需要寻找更优治疗方案^[6]。中医学认为,HSPN属于"水肿"、"发斑"、"尿血"等范畴,其发病机理与瘀血和血热具有密切关系,同时与"溢"产生因果,血热妄行,致瘀阻脉络,属于本虚标实之证^[7]。研究发现^[8],补阳还五汤常用于治疗冠心病、小儿麻痹后遗症,以及其他原因引起的气虚血瘀者,与HSPN发病机理相符,但是否能够提升HSPN治疗效果尚无确切定论。因此,本研究选取我院86例过敏性紫癜性肾炎患儿作为研究对象,探讨补阳还五汤联合西药治疗小儿过敏性紫癜性肾炎的疗效及对机体内皮功能的影响,具体报道如下。

1 资料与方法

1.1 一般资料

选取我院2019年1月到2022年12月收治的86例过敏性紫癜性肾炎患儿作为研究对象,应用随机数字表法将其分为观察组与对照组,每组43例。其中对照组患儿中男23例,女22例;年龄为5-16岁,平均 (11.25 ± 2.36) 岁;过敏性紫癜肾炎病程为1-5个月,平均 (2.23 ± 0.42) 个月;ISKDC分级为I级的11例,II级的28例,III级的6例。观察组患儿中男性25例,女性20例;年龄为5-16岁,平均 (11.63 ± 2.14) 岁;过敏性紫癜肾炎病程为1-4个月,平均 (2.16 ± 0.35) 个月;ISKDC分级为I级的8例,II级的32例,III级的5例。两组患儿一般资料对比无差异($P > 0.05$),具有可比性。本研究经我院伦理委员会批注。

1.2 纳排标准

纳入标准:符合《紫癜性肾炎的诊治循证指南(2016年)》^[9]关于过敏性紫癜肾炎的诊断标准,即在过敏性紫癜发病6个月

内,出现蛋白尿和血尿现象;年龄为5-16周岁;首次发病,并在肾穿刺活检前未经过相关治疗;ISKDC分级为I-III级;蛋白尿 $> 40 \text{ mg/h/m}^2$ 体表面积或蛋白尿呈+++以上;患儿家属对本研究知情并签署同意书。

排除标准:对本研究所用药物过敏者;心肾功能明显异常者;通过肾病活检显示肾脏呈现慢性病理改变者;合并其他慢性疾病或感染者;不配合研究或中途退出者。

1.3 方法

对照组:采取常规对症治疗,其中包括抗过敏、抗感染、潘生丁、维生素C、葡萄糖酸钙、去除诱因等。并清晨口服泼尼松(生产企业:天津市津津药业有限公司;国药准字:H12020036),每日1次,每日剂量为 $1-2 \text{ mg/kg/日}$,口服2-4周逐渐减量,共服用1-2个月。同时静脉注射环磷酰胺(生产企业:Baxter Oncology GmbH;国药准字:H20120181),每日1次,每次 10 mg/kg ,治疗2d之后间隔2周进入到下一个治疗疗程,共治疗1个月。

观察组:在对照组基础上联合补阳还五汤治疗,药方为:黄芪(生)120g,当归尾6g,赤芍5g,地龙(去土)、川芎、红花、桃仁各3g。此为1剂药量,每日1剂,用水煎服,分早晚两次服用。连续治疗3个月后评价两组患者治疗效果。

1.4 观察指标与疗效判定标准

1.4.1 观察指标 (1)肾功能:分别于患者治疗前和治疗3个月后抽取所有患者清晨空腹静脉血5mL,检测明胶酶相关脂质运载蛋白(NGAL)、血肌酐(SCr)、血尿素氮(BUN)表达水平。

(2)炎症因子:采取患者治疗前和治疗后3个月分别在清晨采取两组患者的空腹静脉血5毫升,经过离心之后取上层清液,应用酶联免疫吸附法检测转化生长因子- $\beta 1$ (TGF- $\beta 1$)、白细胞介素-18(IL-18)和白细胞介素-6(IL-6)水平。

(3)血管内皮功能与凝血功能:两组患儿在治疗前后分别空腹采5mL静脉血,以2000 r/min的转速,离心15 min将血清分离。随即在冷藏室保存待用。使用免疫比浊法,试剂盒由南京博研生物科技有限公司提供,检测两组患儿治疗前后D-二聚体和纤维蛋白原(FIB)水平变化。并取下层血浆,应用放射免疫法检测一氧化氮(NO)和内皮素-1(ET-1)表达水平。

1.4.2 疗效判定标准 治疗后患儿关节、胃肠道、皮肤、肾脏受累等状况明显减轻,通过连续3次尿蛋白测定蛋白尿 $< 4 \text{ mg/h/m}^2$ 体表面积或尿蛋白呈阴性为显效;患儿关节、胃肠道、皮肤、肾脏受累等状况有所缓解,血清白蛋白浓度增加超过 35 g/L ,通过连续3次尿蛋白测定蛋白尿降低到 $4-40 \text{ mg/h/m}^2$ 体表面积或尿蛋白仍然为+++以上为无效。总有效率=显效率+有效率^[10]。

1.5 统计学方法

采取 SPSS 23.0 分析,计数资料以(n%)表示,进行 χ^2 检验;计量资料用($\bar{x} \pm s$)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 临床疗效对比

观察组治疗总有效率较对照组高($P < 0.05$),如表 1 所示。

表 1 治疗效果对比(n,%)

Table 1 Comparison of treatment effects (n,%)

Groups	n	Excellence	Valid	Invalid	Total effective rate
Observation group	43	16(37.21%)	23(53.49%)	4(9.30%)	39(90.70%)
Matched group	43	12(27.91%)	18(41.86%)	13(30.23%)	30(69.77%)
χ^2					5.939
P					0.015

2.2 肾功能指标对比

两组患儿治疗前 NGAL、SCr、BUN 对比无明显差异 ($P >$

0.05),治疗后两组患儿 NGAL、SCr、BUN 水平均升高,观察组高于对照组($P < 0.05$),如表 2 所示。

表 2 肾功能指标对比($\bar{x} \pm s$)

Table 2 Kidney function indicators versus($\bar{x} \pm s$)

Groups	n	NGAL($\mu\text{g/L}$)		SCr($\mu\text{mol/L}$)		BUN(mmol/L)	
		Pretherapy	Post-treatment	Pretherapy	Post-treatment	Pretherapy	Post-treatment
Observation group	43	3.55 $\pm$ 1.25	6.58 $\pm$ 2.12*	73.94 $\pm$ 11.49	88.59 $\pm$ 12.24*	6.41 $\pm$ 1.35	11.87 $\pm$ 1.55*
Matched group	43	3.78 $\pm$ 1.37	5.36 $\pm$ 1.15*	73.62 $\pm$ 14.11	81.12 $\pm$ 11.64*	6.26 $\pm$ 1.24	7.83 $\pm$ 1.56*
t	-	0.656	2.677	0.093	2.452	0.433	5.251
P	-	0.515	0.010	0.926	0.024	0.667	0.001

Note: compared with Pretherapy, * $P < 0.05$, The same below.

2.3 炎症因子水平对比

两组患儿治疗前 TGF- β 1、IL-18 和 IL-6 相关炎症因子水平对比无明显差异 ($P > 0.05$),治疗后观察组患儿 TGF- β 1、

IL-18 和 IL-6 相关炎症因子水平低于对照组($P < 0.05$),如表 3 所示。

表 3 炎症因子对比($\bar{x} \pm s$, ng/mL)

Table 3 Comparison of Inflammatory factors ($\bar{x} \pm s$, ng/mL)

Groups	n	TGF- β 1		IL-18		IL-6	
		Pretherapy	Post-treatment	Pretherapy	Post-treatment	Pretherapy	Post-treatment
Observation group	43	202.97 $\pm$ 38.02	142.34 $\pm$ 28.54*	11.02 $\pm$ 2.50	4.08 $\pm$ 1.12*	4.90 $\pm$ 1.29	2.21 $\pm$ 0.98*
Matched group	43	200.13 $\pm$ 37.87	175.59 $\pm$ 32.40*	11.31 $\pm$ 2.48	7.49 $\pm$ 2.09*	5.03 $\pm$ 1.30	3.23 $\pm$ 1.03*
t	-	0.272	3.327	0.582	9.430	0.058	3.171
P	-	0.786	0.001	0.562	0.001	0.954	0.002

2.4 血管内皮功能与凝血功能相关指标对比

两组患儿治疗前 D-二聚体、FIB、NO 和 ET-1 水平对比无差异($P > 0.05$),治疗后观察组患儿 D-二聚体、FIB 和 ET-1 水平均降低,且观察组较对照组低,NO 水平升高,观察组高于对照组($P < 0.05$),如表 4 所示。

3 讨论

当前临床上对于 HSPN 治疗方案尚无明确定论,一般对于轻症患儿国内主张早期预防治疗,而国外则主张对患儿进行定期随访与观察^[1]。国外研究表明^[12],对于大量尿蛋白 HSPN 治疗

应用环孢素 A 的治疗效果优于甲泼尼龙,而应用强的松治疗优于环孢素 A。当前国内对于 HSPN 多选择甲基强的松龙进行治疗,安全性较高,而且能够减轻患儿临床症状,但是对于蛋白尿的影响效果有限^[13]。补阳还五汤为理血剂,具有补气,活血,通络之功效。主治中风之气虚血瘀证。半身不遂,口眼歪斜,语言謇涩,口角流涎,小便频数或遗尿失禁,舌暗淡,苔白,脉缓无力^[14]。中医学认为,小儿乃稚阴稚阳之体,先天禀赋不足,可反复出现血尿及蛋白尿,使病情难愈,故我们采用补阳还五汤进行治疗,希望为 HSPN 的治疗提供一定思路^[15]。

表 4 血管内皮功能与凝血功能相关指标对比($\bar{x} \pm s$)
Table 4 Comparison of vascular endothelial function and coagulation function($\bar{x} \pm s$)

Groups	n	D-dimer(mg/L)		FIB(g/L)		NO(μ mol/L)		ET-1(ng/L)	
		Pretherapy	Post-treat- ment	Pretherapy	Post-treat- ment	Pretherapy	Post-treat- ment	Pretherapy	Post-treat- ment
Observation group	43	5.34 $\pm$ 1.18	2.31 $\pm$ 0.45*	6.58 $\pm$ 1.49	4.31 $\pm$ 1.32*	4.28 $\pm$ 1.21	6.37 $\pm$ 1.26*	75.87 $\pm$ 12.55	55.41 $\pm$ 8.35*
Matched group	43	5.29 $\pm$ 1.16	3.66 $\pm$ 0.51*	6.61 $\pm$ 1.52	5.25 $\pm$ 1.48*	4.37 $\pm$ 1.32	5.32 $\pm$ 1.34*	75.83 $\pm$ 11.56	65.06 $\pm$ 9.24*
t	-	0.198	17.137	0.248	19.895	0.503	3.743	0.215	2.259
P	-	0.844	0.001	0.805	0.001	0.616	0.001	0.830	0.025

本研究结果表明,观察组治疗总有效率较对照组高($P<0.05$)。提示补阳还五汤联合西药治疗 HSPN 临床疗效显著,与赵拖利等^[16]研究相似。以往研究中虽然无补阳还五汤治疗 HSPN 的相关研究,但赵拖利等研究发现,采取自拟清热凉血解毒方可提升 HSPN 的临床疗效,这主要是因为自拟清热凉血解毒方主要是应用中药成分,进行活血散瘀,改善凝血功能,进而提升 HSPN 临床疗效,与本研究补阳还五汤治疗机理相符^[17]。补阳还五汤由中风之后,正气亏虚,气虚血滞,脉络瘀阻所致。正气亏虚,不能行。血以致脉络瘀阻,筋脉肌肉失去濡养,故见半身不遂、口眼喎斜。治当以补气为主,活血通络为辅。本方重用生黄芪,补益元气,意在气旺则血行,瘀去络通,为君药^[18]。当归尾活血通络而不伤血,用为臣药。赤川芎、桃仁、红花协同当归尾以活血祛瘀;地龙通经活络,力专善走,以行药力,亦为佐药^[19]。诸药合用进一步达到活血散瘀通络之效,进而提升 HSPN 的临床疗效;治疗后两组患儿 NGAL、SCr、BUN 水平均升高,观察组较对照组高($P<0.05$)。NGAL、SCr、BUN 为临床上常见的肾功能评价标志物,其中 NGAL 属于某些上皮细胞与中性粒细胞表达的转铁蛋白,属于早期肾损伤标志物,且敏感性较高^[20,21]。而观察组 NGAL、SCr、BUN 高于对照组,也提示了采取补阳还五汤联合西药治疗可提升 HSPN 患儿的肾功能,与吴红胜等^[22]研究相符。吴红胜等研究发现,采取中西医结合治疗 HSPN 能够进一步改善患儿肾功能水平。这可能是因为补阳还五汤中的黄芪、红花、当归、桃仁等成分所致。现代药理学研究表明,当归、红花、桃仁等可改善人体微循环,促进肾小球的血流量增加,而黄芪中所含有的丰富硒元素能够保护肾小球电荷屏障与基底膜机械屏障,进而减少尿蛋白现象,改善肾功能;两组患儿治疗前 TGF- β 1、IL-18 和 IL-6 相关炎症因子水平对比无明显差异($P>0.05$),治疗后观察组患儿 TGF- β 1、IL-18 和 IL-6 相关炎症因子水平低于对照组($P<0.05$)。如果机体出现创伤或感染科迅速增加 TGF- β 1、IL-18 和 IL-6 等炎症因子水平。其中 IL-18 和 IL-6 可反映机体损伤后组织感染情况^[23]。TGF- β 1 会促进炎症因子分泌,可代表病情严重程度^[24]。而观察组患儿 TGF- β 1、IL-18 和 IL-6 水平低于对照组,也证明了采取补阳还五汤联合西药治疗小儿过敏性紫癜性肾炎可降低患儿机体炎症因子水平,改善患儿病情严重程度,与 Zhang J 等^[25]研究相符;治疗后观察组患儿 D-二聚体、FIB 和 ET-1 水平均降低,且观察组较对照组低,NO 水平升高,观察组较对照组高($P<0.05$)。在过敏性紫癜发病过程当中,不仅仅是因为免疫功

能紊乱导致的炎症反应而发病,除此之外,补体激活、免疫复合物沉淀以及血小板聚集与活化也在发病过程中起着重要作用^[26]。这些病理改变可直接激活纤溶系统以及改变凝血功能,从而加重病情。过敏性紫癜患儿的凝血纤溶系统紊乱,可引发 D-二聚体、FIB 表达量升高从而导致相关疾病发生^[27]。另外,过敏性紫癜的发生伴随着多种细胞因子的参与,研究发现^[28],过敏性紫癜患儿机体会出现内皮功能损伤现象,同时机体内的 NO 受体、内皮素与血管内皮生长因子结合形成相互促进作用,共同促进血管炎症反应发生,加重过敏性紫癜病情,导致肾病的发生。而观察组患者 D-二聚体、FIB 和 ET-1 低于对照组,NO 水平高于对照组也证明了采取补阳还五汤治疗能够改善患儿血管内皮功能,提升凝血功能,进一步辅助改善其临床治疗效果,与王峥等^[29]、薛亚楠等^[30]研究相符。

综上所述,补阳还五汤联合西药治疗小儿过敏性紫癜性肾炎临床疗效显著,能够改善患儿肾功能,降低机体炎症反应,提升凝血功能的同时,进一步改善患儿血管内皮功能,值得临床应用推广。但由于本样本量过少,而且对患儿随访时间较少,研究可能存在一定局限,因此还需在日后研究中增加样本量与随访时间进行持续深入研究。

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