

doi: 10.13241/j.cnki.pmb.2020.17.035

玉屏风颗粒联合他克莫司对原发性肾病综合征患儿肾功能、免疫功能以及 Th1/Th2 细胞平衡的影响 *

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摘要 目的:探讨玉屏风颗粒联合他克莫司对原发性肾病综合征(PNS)患儿肾功能、免疫功能以及 Th1/Th2 细胞平衡的影响。**方法:**选取 2017 年 1 月~2019 年 6 月期间我院收治的 PNS 患儿 97 例,根据随机数字表法将患者分为对照组(n=48)和研究组(n=49),对照组患儿给予他克莫司治疗,研究组在对照组的基础上联合玉屏风颗粒治疗,比较两组患儿疗效、肾功能指标[尿素氮(BUN)、血肌酐(Scr)、免疫功能指标[CD3⁺、CD4⁺/CD8⁺、免疫球蛋白 G(IgG)、免疫球蛋白 A(IgA)]以及 Th1/Th2 细胞平衡因子[Th1 细胞分泌的白细胞介素-2(IL-2)、转化生长因子-β1(TGF-β1)及 Th2 细胞分泌的白介素-6(IL-6)、白介素-10(IL-10)],记录两组治疗期间不良反应发生情况。**结果:**研究组治疗 9 个月后的临床总有效率为 91.84%(45/49),高于对照组的 75.00%(36/48)($P<0.05$)。两组治疗 9 个月后 Scr、BUN 均下降,且研究组低于对照组($P<0.05$)。两组治疗 9 个月后 CD3⁺、CD4⁺/CD8⁺、IgG、IgA 均升高,且研究组高于对照组($P<0.05$)。两组不良反应发生率比较无差异($P>0.05$)。两组治疗 9 个月后 TGF-β1、IL-2、IL-10、IL-6 均下降,且研究组低于对照组($P<0.05$)。**结论:**玉屏风颗粒联合他克莫司治疗 PNS 患儿,疗效显著,可有效改善患儿肾功能、免疫功能以及 Th1/Th2 细胞平衡,且不增加不良反应发生率,安全可靠。

关键词:玉屏风颗粒;他克莫司;原发性肾病综合征;肾功能;免疫功能;Th1/Th2 细胞

中图分类号:R692.5 **文献标识码:**A **文章编号:**1673-6273(2020)17-3354-04

Effect of Yupingfeng Granule Combined with Tacrolimus on Renal Function, Immune Function and Th1/Th2 Cell balance in Children with Primary Nephrotic Syndrome*

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ABSTRACT Objective: To investigate the effect of Yupingfeng granule combined with tacrolimus on renal function, immune function and Th1/Th2 cell balance in children with primary nephrotic syndrome (PNS). **Methods:** 97 children with PNS who were admitted to our hospital from January 2017 to June 2019 were selected, they were randomly divided into two groups: control group (n=48) and study group (n=49). The control group was treated with tacrolimus, and the study group was treated with Yupingfeng Granule on the basis of the control group. The curative effect and renal function indexes [urea nitrogen (BUN), blood creatinine (Scr)], immune function indexes [CD3⁺, CD4⁺/CD8⁺, immunoglobulin G (IgG), immunoglobulin A (IGA)] and Th1/Th2 cell balance factor [interleukin-2 (IL-2), transforming growth factor-β1 (TGF-β1), interleukin-6 (IL-6), interleukin-10 (IL-10)] of the two groups were compared, and adverse reactions during treatment were recorded. **Results:** The total clinical effective rate of the study group was 91.84% (45/49), which was higher than 75.00% (36/48) of the control group ($P<0.05$). 9 months after treatment, Scr and BUN decreased in the two groups, and the study group was lower than the control group ($P<0.05$). 9 months after treatment, CD3⁺, CD4⁺/CD8⁺, IgG and IgA in the two groups were all increased, and those in the study group were higher than those in the control group ($P<0.05$). There was no difference in the incidence of adverse reactions between the two groups ($P>0.05$). 9 months after treatment, TGF-β1, IL-2, IL-10 and IL-6 decreased in both groups, and the study group was lower than the control group. **Conclusion:** Yupingfeng granule combined with tacrolimus can improve the renal function, immune function and Th1/Th2 cell balance of children with PNS. It is safe and reliable.

Key words: Yupingfeng granule; Tacrolimus; Primary nephrotic syndrome; Renal function; Immune function; Th1/Th2 cell

Chinese Library Classification(CLC): R692.5 **Document code:** A

Article ID: 1673-6273(2020)17-3354-04

前言

原发性肾病综合征(Primary nephrotic syndrome, PNS)是指肾小球基底膜通透性增加导致大量蛋白质从尿液中漏出的临

* 基金项目:四川省卫生健康委员会科研基金项目(19PJ020)

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(收稿日期:2020-03-23 接受日期:2020-04-18)

床综合征,是儿科常见的泌尿系统疾病。该病临床主要表现为大量蛋白尿、低蛋白血症、高脂血症及不同程度的水肿,严重威胁患儿身心健康^[1-3]。现临床针对该病多以激素治疗为主,他克莫司属于大环内脂类抗生素,既往常用于 PNS 的治疗中,可有效减轻肾脏损伤^[4,5]。然而激素治疗大量应用副作用较多,停药后极易复发,且易产生耐药性,降低患儿用药依从性^[6]。PNS 病因和发病机制尚未完全清楚,既往多认为与细胞免疫功能紊乱有关^[7]。玉屏风颗粒既往常用于治疗非特异性免疫功能低下类疾病以及各种感染,可获得较好的疗效^[8]。本研究通过对我院收治的部分 PNS 患儿给予玉屏风颗粒联合他克莫司治疗,疗效显著,报道如下。

1 资料与方法

1.1 一般资料

纳入标准:(1)PNS 的诊断符合 2000 年全国儿科肾病综合征专题学术研讨会珠海会议制定的诊断标准^[9];(2)患儿家属知情本研究且签署同意书;(3)年龄 4~11 岁;排除标准:(1)合并心肝肺等重要脏器功能不全者(2)入组前曾接受过其他治疗者;(3)伴有乙肝、狼疮性肾炎、紫癜性肾炎、先天性肾病综合征等病变者;(4)对本次研究用药存在过敏症者;(5)治疗前有感染症状者。本次研究已通过我院伦理学委员会批准进行。选取 2017 年 1 月~2019 年 6 月期间我院收治的 PNS 患儿 97 例,根据随机数字表法将患儿分为对照组($n=48$)和研究组($n=49$),其中对照组男 28 例,女 20 例,年龄 4~11 岁,平均(7.26 ± 0.82)岁;病程 4~23 月,平均(13.49 ± 2.49)月;临床分型:肾炎性肾病 22 例,单纯性肾病 26 例;肾活检类型:微小病变 17 例,系膜增生型肾炎 18 例,局灶节段型肾小球硬化 13 例。研究组男 31 例,女 18 例,年龄 4~10 岁,平均(7.14 ± 1.06)岁;病程 5~22 月,平均(13.26 ± 1.98)月;临床分型:肾炎性肾病 20 例,单纯性肾病 29 例;肾活检类型:微小病变 17 例,局灶节段型肾小球硬化 10 例,系膜增生型肾炎 22 例。两组一般资料对比无差异($P>0.05$)。

1.2 方法

两组均给予常规对症治疗,包括降低血压、平衡电解质、利尿、抗感染等,在此基础上,对照组给予他克莫司(国药准字

H20084386,浙江海正药业股份有限公司,规格:0.5 mg)治疗,初始剂量为 0.10 mg/(kg·d),2 次/d,服用间隔 12 h。研究组在对照组基础上联合玉屏风颗粒[国药准字 Z10930036,国药集团广东环球制药有限公司,规格:每袋装 5 g(相当于饮片 10 g)]治疗,5 g/次,3 次/d。两组患儿均连续治疗 9 个月。

1.3 观察指标

(1)记录两组临床疗效 疗效判定标准如下:治愈:肾病综合征症状完全消失,Alb 及肾功能恢复正常,24 h 尿蛋白定量 <0.15 g;显效:肾病综合征症状基本消失,Alb 改善明显,肾功能接近正常,24 h 尿蛋白定量 <25 mg/kg;有效:Alb 有所缓解,肾功能有所好转,25 mg/kg <24 h 尿蛋白定量 <50 mg/kg;无效:肾病综合征症状依然存在,Alb 及肾功能未见变化,24 h 尿蛋白定量 >50 mg/kg。总有效 = 治愈 + 显效 + 有效^[10]。(2)抽取患儿治疗前、治疗 9 个月后的空腹肘静脉血 6 mL,分为三管,一管采用美国库尔特公司(COULTER)生产的 EPICSXL 流式细胞仪检测 T 淋巴细胞亚群指标:CD3⁺、CD4⁺/CD8⁺ 水平。一管采用深圳迈瑞公司生产的 MINDRAY BS420 型全自动生化分析仪检测血清免疫球蛋白 G(IgG)、免疫球蛋白 A(IgA)。最后一管经常规离心处理(3200 r/min 离心 12 min,离心半径 10 cm),分离上清液,置于冰箱(-20℃)中待测。参考试剂盒(上海玉博生物科技有限公司)说明书步骤,采用尿素酶法测定尿素氮(BUN),采用双缩脲法测定血肌酐(Scr)。采用酶联免疫吸附法检测 Th1 细胞分泌的白细胞介素 -2(IL-2)、转化生长因子 - β 1(TGF- β 1) 及 Th2 细胞分泌的白介素 -6(IL-6)、白介素 -10(IL-10)水平。(3)记录不良反应。

1.4 统计学方法

应用 SPSS27.0 软件进行统计学分析,计量资料以($\bar{x} \pm s$)表示,采用 t 检验。计数资料以[n(%)]表示,采用 χ^2 检验。 $P<0.05$ 为差异具有统计学意义。

2 结果

2.1 疗效比较

研究组治疗 9 个月后的临床总有效率为 91.84%(45/49),高于对照组的 75.00%(36/48)($P<0.05$);详见表 1。

表 1 两组临床疗效比较 例(%)
Table 1 Comparison of clinical effects between the two groups n(%)

Groups	Cure	Effective	Better	Invalid	Total efficiency
Control group($n=48$)	8(16.67)	16(33.33)	12(25.00)	12(25.00)	36(75.00)
Study group($n=49$)	12(24.49)	20(40.82)	13(26.53)	4(8.16)	45(91.84)
χ^2					4.990
P					0.025

2.2 肾功能指标比较

两组治疗前 Scr、BUN 比较无差异($P>0.05$);两组治疗 9 个月后 Scr、BUN 均下降,且研究组低于对照组($P<0.05$);详见表 2。

2.3 免疫功能指标比较

两组治疗前 CD3⁺、CD4⁺/CD8⁺、IgG、IgA 比较无差异($P>0.$

05);两组治疗 9 个月后 CD3⁺、CD4⁺/CD8⁺、IgG、IgA 均升高,且研究组高于对照组($P<0.05$);详见表 3。

2.4 Th1/Th2 细胞平衡因子比较

两组治疗前 IL-2、TGF- β 1、IL-6、IL-10 比较差异无统计学意义($P>0.05$);两组治疗 9 个月后 IL-2、TGF- β 1、IL-6、IL-10 均下降,且研究组低于对照组($P<0.05$);详见表 4。

表 2 肾功能指标比较($\bar{x} \pm s$, mmol/L)
Table 2 Comparison of renal function indexes($\bar{x} \pm s$, mmol/L)

Groups	Scr		BUN	
	Before treatment	9 months after treatment	Before treatment	9 months after treatment
Control group(n=48)	8.85± 1.36	6.36± 1.83*	96.31± 8.72	69.72± 7.69*
Study group(n=49)	8.79± 1.03	4.07± 0.97*	96.84± 9.60	45.63± 6.21*
t	0.245	7.722	0.284	16.991
P	0.807	0.000	0.777	0.000

表 3 两组免疫功能指标比较($\bar{x} \pm s$)
Table 3 Comparison of immune function indexes between the two groups($\bar{x} \pm s$)

Groups	CD3 ⁺ (%)		CD4 ⁺ /CD8 ⁺		IgG(g/L)		IgA(g/L)	
	Before treatment	9 months after treatment	Before treatment	9 months after treatment	Before treatment	9 months after treatment	Before treatment	9 months after treatment
Control group(n=48)	35.20± 6.35	42.33± 6.27*	1.31± 0.28	1.59± 0.36*	4.41± 1.29	7.79± 1.32*	0.82± 0.19	1.06± 0.23*
Study group(n=49)	35.68± 5.29	48.75± 7.34*	1.28± 0.22	1.82± 0.25*	4.46± 1.05	10.07± 1.25*	0.79± 0.22	1.41± 0.26*
t	0.405	4.627	0.587	3.661	0.210	8.736	0.718	7.017
P	0.687	0.000	0.558	0.000	0.834	0.000	0.474	0.000

Note: compared with before treatment, * $P < 0.05$.

表 4 两组 Th1/Th2 细胞平衡因子比较($\bar{x} \pm s$, ng/L)
Table 4 Comparison of Th1/Th2 cell balance factors between the two groups($\bar{x} \pm s$, ng/L)

Groups	IL-2		TGF- β 1		IL-6		IL-10	
	Before treatment	9 months after treatment	Before treatment	9 months after treatment	Before treatment	9 months after treatment	Before treatment	9 months after treatment
Control group(n=48)	2.59± 0.32	2.21± 0.27*	143.59± 19.56	86.58± 12.39*	4.16± 0.49	2.79± 0.37*	13.20± 2.95	8.73± 2.71*
Study group(n=49)	2.55± 0.21	1.96± 0.25*	142.64± 20.47	73.82± 9.21*	4.12± 0.41	1.56± 0.24*	13.08± 2.88	5.35± 1.64*
t	0.729	4.733	0.234	5.765	0.436	19.464	0.203	7.449
P	0.468	0.000	0.816	0.000	0.664	0.000	0.804	0.000

Note: compared with before treatment, * $P < 0.05$.

2.5 不良反应发生率比较

治疗期间,对照组发生 2 例感染、1 例胃肠道不适、1 例水钠潴留,不良反应发生率为 8.33%(4/48);研究组发生 2 例胃肠道不适、3 例感染、1 例水钠潴留,不良反应发生率为 12.24%(6/49);两组不良反应发生率比较差异无统计学意义($\chi^2=0.401$, $P=0.526$)。

3 讨论

PNS 的病因及发病机制未明,以往多认为 PNS 的发生与免疫功能异常关系密切^[11,12]。当机体处于正常状态时,各 T、B 细胞亚群相互作用、遗传免疫以及各种免疫球蛋白构成免疫网络,维持着机体的正常免疫功能,抵抗各类感染、细菌及病毒^[13]。研究表明^[14,15],CD4⁺/CD8⁺ 平衡具有免疫调节功能,其失衡可激活机体免疫抑制反应。CD4⁺T 细胞可分 Th1 与 Th2,活化的 Th2 细胞分泌 IL-10、IL-6 等细胞因子,活化的 Th1 细胞分泌

TGF- β 1、IL-2 等细胞因子,提示 Th1/Th2 失衡可能也与 PNS 的发生与发展关系密切^[16-18]。由于儿童时期免疫系统发育尚未完善,自身免疫力偏低,经大量激素治疗后感染风险显著提升,若患儿感染,可能影响相关信号通路而阻止靶细胞对激素的效应,导致药效降低,病情反复发作^[19,20]。他克莫司是强效免疫抑制剂,可缓解机体免疫介导的炎症反应,抑制 CD4⁺T 细胞活化,有效改善患者蛋白尿的症状,同时还可减轻炎症介质对肾脏尤其是肾小球的损伤^[21-23]。但是他克莫司的副作用如感染可能会加重疾病的进展。

玉屏风颗粒出自元·朱丹溪的《丹溪心法》,具有益气固表、扶正固本之效^[24]。本研究在他克莫司的基础上联合玉屏风颗粒治疗,结果显示,研究组治疗 9 个月后的疗效优于对照组,可见玉屏风颗粒联合他克莫司治疗 PNS 患儿,可进一步提高治疗效果。玉屏风颗粒的主要成分为白术、黄芪、防风等,其中白术的主要成分为白术醇,并含有少量维生素 A,发挥抗炎、抗惊

厥、提高免疫等作用,同时还可有效增强肠壁的吸收作用^[25]。黄芪含有多种氨基酸、叶酸及微量元素,可促进免疫球蛋白的产生,增强网状内皮细胞吞噬能力及增强细胞免疫功能^[26]。防风的总多糖可作用于肠道黏膜,通过影响黏膜免疫系统进而改善全身免疫^[27]。玉屏风颗粒联合他克莫司治疗可发挥协同作用,促进免疫功能改善,进一步提高治疗效果。T淋巴细胞是机体细胞免疫主要的组成部分,PNS患儿存在CD3⁺、CD4⁺表达受到抑制,Th1/Th2细胞平衡失衡情况。而PNS患儿的免疫功能紊乱可作用于肾脏组织,引起肾损伤,导致肾小球的滤过膜的膜通透性改变,IgG、IgA等小分子蛋白质会通过滤过膜进入尿液排出体外,导致机体大量蛋白质流失^[28]。本研究玉屏风颗粒联合他克莫司治疗可有效改善患儿肾功能、免疫功能以及Th1/Th2细胞平衡,可能是因为玉屏风颗粒具有增加淋巴细胞的作用,进而调节T淋巴细胞亚群,促使CD4⁺/CD8⁺比值以及Th1/Th2细胞恢复至正常,改善了人体免疫功能,促使免疫系统平稳,减轻其对机体肾脏功能的损害,提高机体抗感染、抗病毒能力^[29]。另两组不良反应发生率比较差异无统计学意义,可见上述联合治疗方案安全可靠。而刘钧菲等^[30]研究认为,玉屏风颗粒增强了PNS患儿的抵抗力,可显著降低不良反应的发生。这与本次研究结果不一致,可能是因为本次研究样本量较少,且存在个体性差异,后续报道将扩大样本量、延长随访观察时间,以获取更为准确的数据。

综上所述,PNS患儿在他克莫司治疗的基础上联合玉屏风颗粒,可有效改善患儿肾功能、免疫功能以及Th1/Th2细胞平衡,且不增加不良反应发生率,安全可靠,疗效显著。

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