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肾康注射液联合羟苯磺酸钙胶囊对 PNS 并发 AKI 患者肾功能、凝血功能及炎性因子的影响 *

陈 琳[1] 黄 洁[1] 陈滢洁[1] 沈 君[1△] 王 晶[2]

（1 上海交通大学医学院附属第九人民医院肾脏内科 上海 200011；2 复旦大学附属中山医院肾内科 上海 200032）

摘要 目的：探讨肾康注射液联合羟苯磺酸钙胶囊对原发性肾病综合征（PNS）并发急性肾损伤（AKI）患者肾功能、凝血功能及炎性因子的影响。**方法：**选取 2018 年 4 月 ~2019 年 11 月期间我院收治的 134 例 PNS 合并 AKI 患者，随机分为对照组（常规治疗基础上予以羟苯磺酸钙胶囊治疗）和联合组（对照组基础上予以肾康注射液治疗），各 67 例。治疗 14 d 后，对比两组患者疗效、肾功能指标[尿素氮（BUN）、血肌酐（Scr）、白蛋白（Alb）]、凝血功能指标[凝血酶时间(TT)、凝血酶原时间（PT）、活化部分凝血酶原时间(APTT)、纤维蛋白原(FIB)]及炎性因子[白介素 -6(IL-6)、肿瘤坏死因子 -α(TNF-α)、C 反应蛋白(CRP)]，记录两组不良反应情况。**结果：**联合组治疗 14d 后的临床总有效率高于对照组（P<0.05）。治疗 14 d 后，两组 PT、APTT、TT、FIB、Scr、BUN、IL-6、TNF-α、CRP 均较治疗前下降，且联合组低于对照组（P<0.05）。治疗 14 d 后，两组 Alb 升高，且联合组高于对照组（P<0.05）。对照组、联合组的不良反应总发生率对比未见统计学差异（P>0.05）。**结论：**相较于羟苯磺酸钙胶囊单药治疗，PNS 合并 AKI 患者在羟苯磺酸钙胶囊的基础上联合肾康注射液治疗，可有效减轻肾功能损害，改善凝血功能，降低炎性因子水平，疗效明显，且未增加严重不良反应。

关键词：肾康注射液；羟苯磺酸钙胶囊；原发性肾病综合征；急性肾损伤；肾功能；凝血功能；炎性因子

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Effect of Shenkang Injection Combined with Calcium Dobesilate Capsule on Renal Function, Coagulation Function and Inflammatory Factors in Patients with PNS Complicated with AKI*

CHEN Lin[1], HUANG Jie[1], CHEN Ying-jie[1], SHEN Jun[1△], WANG Jing[2]

(1 Department of Nephrology, The Ninth People's Hospital Affiliated to Medical School of Shanghai Jiaotong University, Shanghai, 200011, China; 2 Department of Nephrology, Zhongshan Hospital Affiliated to Fudan University, Shanghai, 200032, China)

ABSTRACT Objective: To investigate the effect of Shenkang injection combined with calcium dobesilate capsule on renal function, coagulation function and inflammatory factors in patients with primary nephrotic syndrome (PNS) complicated with acute kidney injury (AKI). **Methods:** From April 2018 to November 2019, 134 patients with PNS complicated with AKI in our hospital were selected, they were randomly divided into control group (treated with calcium dobesilate capsules on the basis of conventional treatment) and combined group (treated with Shenkang injection on the basis of control group), 67 cases in each group. 14 days after treatment, the curative effect, renal function indexes [urea nitrogen (BUN), serum creatinine (Scr), albumin (Alb)], coagulation function indexes [thrombin time (TT), prothrombin time (PT), activated partial prothrombin time (APTT), fibrinogen (FIB)] and inflammatory factors [interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), C-reactive protein (CRP)] were compared between the two groups. The adverse reactions of the two groups were recorded. **Results:** 14 days after treatment, the total effective rate of the combined group was higher than that of the control group (P<0.05). 14 days after treatment, PT, APTT, TT, FIB, Scr, BUN, IL-6, TNF-α and CRP of the two groups decreased compared with those before treatment, and the combined group was lower than the control group (P<0.05). 14 days after treatment, Alb of the two groups increased, and the combined group was higher than the control group (P<0.05). There was no significant difference in the total incidence of adverse reactions between the control group and the combined group(P>0.05). **Conclusion:** Compared with calcium dobesilate capsule single drug treatment, patients with PNS complicated with AKI on the basis of calcium dobesilate capsules combined with Shenkang injection can effectively reduce renal function damage, improve coagulation function, reduce the level of inflammatory factors, with obvious curative effect, and no increase of serious adverse reactions.

Key words: Shenkang injection; Calcium dobesilate capsule; Primary nephrotic syndrome; Acute kidney injury; Renal function; Coagulation function; Inflammatory factors

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作者简介：陈琳（1984-），女，本科，中级，研究方向：肾脏病理，E-mail: chengpanlu0699990@163.com

△ 通讯作者：沈君（1972-），女，本科，中级，研究方向：肾脏病理，E-mail: pig147258369@163.com

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前言

肾病综合征(NS)是一种以肾小球滤过屏障通透性升高、肾小球基底膜损伤、大量蛋白从尿中丢失为病理基础的临床综合征候群，其中原发性肾病综合征（PNS）约占所有 NS 的 75%[1-3]。PNS 临床主要以高蛋白尿、低蛋白血症、血脂升高、凝血障碍、全身炎性反应为主要表现，严重者可出现急性肾损伤(AKI)类并发症[4]。据以往数据报道显示[5]，PNS 患者中 AKI 的发生率可达 6.5%~6.9%，如果不及时治疗干预，可进展为不可逆性的急性肾衰竭，危及患者性命。目前临床有关 PNS 治疗尚无特异性方案，羟苯磺酸钙胶囊是毛细血管保护剂[6]，既往研究显示将其用于 PNS 的治疗，可有效改善肾脏微循环，减轻肾脏损害[7]。然而 PNS 易反复发作，长期大量的西药治疗不良反应较多，造成治疗效果减弱[8]。肾康注射液是国家中药二类新药，临床多用于治疗糖尿病肾病、慢性肾功能衰竭等病症[9]。本研究将肾康注射液联合羟苯磺酸钙胶囊应用于治疗 PNS 合并 AKI 患者，疗效较好，总结如下。

1 资料与方法

1.1 一般资料

选取 2018 年 4 月 ~2019 年 11 月期间我院收治的 PNS 合并 AKI 患者 134 例，纳入标准：(1)患者均符合《原发性肾病综合征的诊断、辨证分型及疗效评定(试行方案)》[10]中 PNS 的诊断标准；(2)符合 AKI 的诊断标准[11]；(3)患者及其家属知情本研究且签署同意书；(4) 配合完成了本研究设计的相关检测；(5)对本研究用药方案耐受。排除标准：(1)糖尿病肾病和过敏性紫癜性肾炎患者；(2)妊娠或哺乳期妇女；(3)恶性肿瘤、严重的心肝功能障碍者、甲状腺疾病、血液系统疾病患者；(4)精神疾病及认知功能不全者；(5)感染性疾病、自身免疫性疾病导致的肾病者。随机分为对照组和联合组，各 67 例。对照组女 38 例，男 29 例，病程 5~22 月，平均(13.56± 2.49)月；年龄 23~63 岁，平均(41.15± 4.27)岁；病理类型：膜性肾病 14 例，系膜增生性肾小球肾炎 17 例，系膜毛细血管性肾炎 21 例，其他 15 例。联合组女 40 例，男 27 例，病程 7~20 月，平均(13.24± 2.31)月；年龄 25~61 岁，平均(41.46± 5.18)岁；病理类型：系膜增生性肾小球肾炎 17 例，系膜毛细血管性肾炎 19 例，膜性肾病 17 例，其他 14 例。两组患者一般资料对比无差异(P>0.05)，具有可比性。研究经我院医学伦理学委员会批准。

1.2 方法

两组均给予保护胃黏膜、维持水电解质酸碱平衡、控制饮食、抗凝、扩容利尿消肿等基础治疗。在此基础上，对照组给予羟苯磺酸钙胶囊(国药准字 H20030088，上海朝晖药业有限公司，规格：0.5 g)口服，1 粒 / 次，3 次 /d。联合组给予羟苯磺酸钙胶囊联合肾康注射液(国药准字 Z20040110，西安世纪盛康药业有限公司，规格：20 mL/ 支)治疗，将肾康注射液 100 mL 溶于 5%葡萄糖注射液 250 mL 静脉滴注，1 次 /d。羟苯磺酸钙胶囊用法用量同对照组。两组均治疗 14 d。

1.3 疗效判定标准

完全缓解：血肌酐(Scr)较基础值有下降，肾实质性水肿、高血压等症状与体征完全消失，尿蛋白持续阴性，尿红细胞持续阴性。基本缓解：尿蛋白及红细胞减少 >50%，症状与体征基本消失，Scr 较基础值无变化或升高 <50%。有效：症状和体征明显好转，尿蛋白及红细胞减少≥ 25%，50%≤ Scr 较基础值升高 < 100%。无效：未达到以上标准。总有效率 = 完全缓解率 + 基本缓解率 + 有效率[10]。

1.4 检测方法

采集两组患者治疗前、治疗 14 d 后的肘静脉血 6 mL，需在空腹状态下取血，经离心处理：离心半径 10 cm，3200 r/min 离心 15 min，分离血清，置于冰箱(-30℃)中待测。采用双缩脲法测定 Scr，采用溴甲酚绿法测定血清白蛋白(Alb)，采用尿素酶法测定尿素氮（BUN），采用酶联免疫吸附试验检测肿瘤坏死因子 -α(TNF-α)、白介素 -6(IL-6)、C 反应蛋白(CRP)水平，严格遵守试剂盒(北京软隆生物技术有限公司)说明书进行操作。采用美国 Beckman-Coulter 公司生产的 ACL-TOP 型全自动凝血分析仪检测凝血功能指标：活化部分凝血酶原时间(APTT)、凝血酶时间(TT)、凝血酶原时间(PT)、纤维蛋白原(FIB)。

1.5 安全性评价

记录两组不良反应。

1.6 统计学方法

应用 SPSS23.0 软件分析数据，计量资料以($\bar{x}\pm s$)表示，两组采用 t 检验。以百分比表示计数资料，采用 x^2 检验。α=0.05 为检验水准。

2 结果

2.1 两组总有效率比较

联合组治疗 14 d 后的临床总有效率 94.03%(63/67）高于对照组的 77.61%(52/67)(P<0.05)，详见表 1。

表 1 两组总有效率比较 [n(%)]

Table 1 Comparison of total effective rate between the two groups [n(%)]

Groups	Complete remission	Basic remission	Effective	Invalid	Total effective rate
Control group(n=67)	11(16.42)	23(34.33)	18(26.87)	15(22.39)	52(77.61)
Combined group(n=67)	17(25.37)	26(38.81)	20(29.85)	4(5.97)	63(94.03)
x^2					7.421
P					0.006

2.2 两组凝血功能指标比较

治疗前，两组 PT、APTT、TT、FIB 对比未见统计学差异(P>0.05)，治疗 14 d 后，两组 PT、APTT、TT、FIB 均下降，且联合组较对照组低(P<0.05)，具体见表 2。

表 2 两组凝血功能指标比较($\bar{x}\pm s$)

Table 2 Comparison of coagulation function indexes between the two groups($\bar{x}\pm s$)

Groups	Time	PT(s)	APTT(s)	TT(s)	FIB(g/L)
Control group(n=67)	Before treatment	20.63± 1.42	47.94± 6.37	23.46± 2.13	6.41± 0.28
	14 d after treatment	16.59± 1.37[a]	38.28± 5.39[a]	19.89± 2.38[a]	5.28± 0.26[a]
Combined group (n=67)	Before treatment	20.09± 1.25	47.56± 6.26	23.23± 2.25	6.36± 0.29
	14 d after treatment	12.36± 0.92[ab]	34.81± 3.29[ab]	15.91± 1.36[ab]	3.96± 0.24[ab]

Note: compared with before treatment, [a]P<0.05; compared with control group, [b]P<0.05.

2.3 两组肾功能指标比较

治疗前，两组 Scr、Alb、BUN 对比未见统计学差异(P>0.05)，治疗 14 d 后，两组 Scr、BUN 均下降，且联合组低于对照组(P<0.05)；Alb 升高，且联合组高于对照组(P<0.05)，具体见表3。

表 3 两组肾功能指标比较($\bar{x}\pm s$)

Table 3 Comparison of renal function indexes between the two groups($\bar{x}\pm s$)

Groups	Time	Scr(μmol/L)	Alb(g/L)	BUN(mmol/L)
Control group(n=67)	Before treatment	135.32± 12.31	18.66± 2.23	11.28± 2.13
	14 d after treatment	96.14± 14.29[a]	26.21± 2.57[a]	7.31± 2.14[a]
Combined group(n=67)	Before treatment	136.81± 15.14	18.19± 2.45	11.47± 1.73
	14 d after treatment	78.05± 13.16[ab]	31.63± 2.58[ab]	4.29± 1.09[ab]

Note: compared with before treatment, [a]P<0.05; compared with control group, [b]P<0.05.

2.4 两组炎性因子指标比较

治疗前，两组炎性因子指标对比未见差异(P>0.05)，治疗 14 d 后，两组 IL-6、TNF-α、CRP 均下降，且联合组低于对照组(P<0.05)，具体见表 4。

表 4 两组炎性因子指标比较($\bar{x}\pm s$)

Table 4 Comparison of inflammatory factors between the two groups($\bar{x}\pm s$)

Groups	Time	IL-6(pg/mL)	TNF-α(ng/mL)	CRP(mg/L)
Control group(n=67)	Before treatment	95.77± 13.36	5.88± 0.57	10.23± 1.17
	14 d after treatment	62.71± 11.29[a]	3.85± 0.48[a]	7.17± 1.24[a]
Combined group(n=67)	Before treatment	95.97± 12.96	5.94± 0.53	10.17± 1.32
	14 d after treatment	39.26± 9.82[ab]	2.54± 0.47[ab]	3.41± 0.98[ab]

Note: compared with before treatment, [a]P<0.05; compared with control group, [b]P<0.05.

2.5 两组安全性评价

对照组、联合组的不良反应总发生率对比未见统计学差异(P>0.05)，详见表 5。

表 5 两组不良反应发生情况 [n(%)]

Table 5 Adverse reactions in the two groups [n(%)]

Groups	Infected	Nausea and vomiting	Gastrointestinal bleeding	Retention of water and sodium	Total incidence
Control group(n=67)	2(2.99)	3(4.48)	1(1.49)	2(2.99)	8(11.94)
Combined group(n=67)	3(4.48)	4(5.97)	2(2.99)	2(2.99)	11(16.42)
x^2					0.552
P					0.458

3 讨论

PNS 可发生于任何年龄段，AKI 是其最严重的并发症之一，其治疗难度大、病死率极高[12,13]。目前有关该病的发病机制尚未完全明确，目前研究认为其发病可能与以下机制有关：低蛋白血症、大量蛋白尿、水钠潴溜于组织间隙等均可致使有效血容量不足，肾血流量减少造成肾损害；肾间质水肿可造成肾内梗阻，肾小管滤过压下降，导致肾小管滤过功能受到影响，进

而加重肾损伤;血管紧张素生成增多,肾素分泌增加,引起肾小动脉收缩,亦会导致肾血流量减少,从而激活了体内的免疫应激,PNS 患者由于免疫复合物诱导的血流动力学异常、炎性反应等影响因素,导致机体凝血、抗凝及纤溶系统失衡,血小板激活,内皮细胞受损,各类脏器微循环障碍,继而并发 AKI[14-16]。

羟苯磺酸钙胶囊是一类醛糖还原酶抑制剂,该药可有效降低人体内山梨醇含量,增强血红蛋白柔韧性,降低毛细血管通透性和脆性,减轻水肿[17,18]。此外,羟苯磺酸钙胶囊还具有抗炎功效,可降低血液黏稠度,恢复循环功能[19,20]。既往研究将羟苯磺酸钙胶囊用于肾病治疗发现,其可舒张肾小球入球小动脉以增加肾脏血流量,有效抑制肾细胞凋亡及基底膜增生[21,22]。随着生物医学模式的转变,中西医结合治疗 PNS 合并 AKI 已成为流行趋势[23]。肾康注射液的主要成分为丹参、黄芪、红花、大黄,其中大黄活血解毒、攻积利湿,红花活血活络通经,黄芪补气升阳、利水消肿,丹参养血安神、活血祛瘀[24]。现代药理研究显示[25]肾康注射液中黄芪可扩张肾动脉血管,增强造血系统功能,改善机体血流量,发挥肾脏保护作用;大黄则能够抑制细胞外基质堆积以及肾脏系膜细胞增生,修复损伤的肾小管上皮细胞,延缓肾小球硬化,从而延缓患者肾脏病的发展;红花能够降低血脂水平并改善血液高凝状态,抗血小板黏附聚集,保护残余肾功能;丹参有降低血黏度 / 降低血脂 / 扩张血管、抑制血小板聚集和释放、改善微循环的作用,并能修复损伤的血管内膜,从而保护和促进肾脏功能的恢复。本研究中,联合组的疗效优于对照组,且肾功能、凝血功能、炎症状态均有所改善,可见羟苯磺酸钙胶囊的基础上联合肾康注射液治疗,疗效明确,可有效阻止疾病进展,可能与羟苯磺酸钙胶囊联合肾康注射液治疗可有效控制机体炎症水平,改善机体内环境,促使机体凝血 - 纤溶系统的平衡逐步恢复有关。其中 PT、APTT、TT、FIB 是反映凝血 - 纤溶系统平衡的常规指标。而 Scr、Alb、BUN 是反映机体肾功能的常见指标。IL-6、TNF-α、CRP 均是临床常见的炎症因子指标,可反映机体炎症严重程度[26];CRP 作为急性时相蛋白的一种,可与脂蛋白结合,产生大量炎症介质,损伤肾血管内膜细胞[27];IL-6 可诱导其他炎性介质分泌,TNF-α 可促进 CRP、IL-6 等生成,这些生物分子可使肾小球系膜细胞和内皮细胞通透性增加,导致肾小球滤过液回渗,加速肾功能损伤[28]。肾康注射液通过降低肾小球毛细血管压力,增加肾血流量,改善肾小球内血液高凝状态,最终达到改善肾功能、降低炎症反应的目的[29,30]。同时对照组、联合组的不良反应总发生率对比无差异,表明该联合治疗方案安全可靠,不会增加严重的不良反应。

综上所述,PNS 合并 AKI 患者在羟苯磺酸钙胶囊的基础上联合肾康注射液治疗,可有效减轻肾功能损害,改善凝血功能,降低炎症因子水平,疗效明显,且未增加严重不良反应。

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