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中西医结合治疗膜性肾病的疗效及机制研究*

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摘要 目的:探究中西医结合对膜性肾病的治疗效果,并就其机制进行研究。**方法:**选择2015年12月至2019年12月于我院接受治疗的98例肾病综合征患者,按照随机数字表法将其均分为研究组与对照组(每组各49例),对照组接受常规西医治疗,研究组在对照组基础上加用中医疗法,对比两组治疗有效率,分别检测并对比治疗前后两组免疫球蛋白A(immunoglobulin A, IgA)、免疫球蛋白G(immunoglobulin G, IgG)、免疫球蛋白M(immunoglobulin M, IgM)、蛋白排泄率(urinary albumin excretion rates, UAER)、血浆白蛋白(albumin, Alb)、尿素氮(blood urea nitrogen, BUN)、血肌酐(serum creatinine, Scr)等指标,并就治疗安全性进行对比。**结果:**(1)研究组治疗有效率显著高于对照组(95.92% vs. 81.63%, $P<0.05$);(2)治疗前两组IgA、IgG、IgM水平对比无统计学意义($P>0.05$),干预后研究组上述指标均优于对照组($P<0.05$);(3)治疗前两组UAER、Alb、BUN及Scr水平对比无统计学意义($P>0.05$),治疗后研究组上述指标均优于对照组($P<0.05$);(4)研究组治疗中不良反应发生率低于对照组($P<0.05$)。**结论:**中西医结合疗法对膜性肾病具有较好的治疗效果,能够显著改善患者免疫功能及肝肾功能,同时还能够降低治疗中不良反应发生率。

关键词: 中西医结合;膜性肾病;疗效;机制研究

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Efficacy and Mechanism of Integrated Traditional Chinese and Western Medicine in Membranous Nephropathy*

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ABSTRACT Objective: To explore the therapeutic effect of integrated traditional Chinese and western medicine on membranous nephropathy and to study its mechanism. **Methods:** 98 patients with membranous nephropathy who were treated in our hospital from December 2015 to December 2019 were selected, and they were divided into study group and control group (49 patients in each group) according to the random number table method. The control group received conventional Western medicine treatment, and the study group were treated with traditional Chinese medicine on the basis of the control group. Compare the treatment effectiveness of the two groups, measure and compare IgA, IgG, IgM, UAER, Alb, BUN, Scr and other indicators before and after treatment, and compare the safety. **Results:** (1) The treatment efficiency of the study group was significantly higher than that of the control group (95.92% vs. 81.63%, $P<0.05$). (2) The levels of IgA, IgG, and IgM in the two groups before treatment were not statistically significant ($P>0.05$). The above indicators in the study group were better than those in the control group after intervention ($P<0.05$). (3) The levels of UAER, Alb, BUN and Scr in the two groups before treatment were not statistically significant ($P>0.05$). The above indicators in the study group were better than those in the control group after treatment ($P<0.05$). (4) The incidence of adverse reactions in the treatment group was lower than that in the control group ($P<0.05$). **Conclusion:** The integrated Chinese and western medicine therapy has a good therapeutic effect on membranous nephropathy, which can significantly improve the immune function and liver and kidney function of patients, and can also reduce the incidence of adverse reactions during treatment.

Key words: Integrated Traditional Chinese and Western Medicine; Membranous nephropathy; Efficacy; Mechanism Study

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前言

肾病综合征是在多种病理因素共同作用下所导致的一类疾病,膜性肾病(membranous nephropathy, MN)是最为常见的病

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理类型,一般不伴肾小球固有细胞增殖和局部炎症反应,其典型临床症状包括肾病综合征(大量蛋白尿、低蛋白血症、高度浮肿、高脂血症),或无症状、非肾病范围的蛋白尿,部分患者伴有镜下血尿、高血压和肾功能损害。膜性肾病发病机制尚未完全阐明,很多系统性疾病以及一些药物和环境因素,均可以导致继发性膜性肾病^[1,2]。临床实践表明,膜性肾病病情不易控制且易反复,在发病过程中呈现进行性发展,直至引发终末期肾功能衰竭,对患者生活质量造成严重影响^[3]。当前西医对膜性肾病的治疗方式主要为应用激素或细胞毒性药物,虽然能够降低蛋白尿水平,使肾功能保持稳定,但仍有 32 % 的患者会复发,同时 66 % 的患者存在较为严重的不良反应,且治疗中大量激素的应用易诱发感染事件,因而当前膜性肾病的治疗重点为寻求联合治疗方案^[4-6]。祖国传统医学中无肾病综合征这一名词,但"水肿"、"虚劳"、"腰痛"、"尿浊"等都属于对该病的描述,中医认为该病的治疗应从"补气益肾"、"温补脾肾"、"益气养阴"等入手,以益气活血、化瘀通络法贯穿治疗始末^[7-9]。本文作者通过研究发现,中西医结合疗法对膜性肾病具有较好的治疗效果,能够显著改善患者免疫功能及肝肾功能,同时还降低治疗中不良反应发生率,现详述如下。

1 资料与方法

1.1 一般资料

选择 2015 年 12 月至 2019 年 12 月于我院接受治疗的 98 例膜性肾病患者,按照随机数字表法将其均分为两组($n=49$),对照组中男性 26 例,女性 23 例,年龄 29-67 岁,平均年龄(50.16 ± 2.66)岁,研究组中男性 25 例,女性 24 例,年龄 30-68 岁,平均年龄(49.97 ± 2.71)岁,两组一般资料对比无差异($P>0.05$),具有可比性。

纳入标准:(1)均符合 2015 年制订的肾病综合征诊断标准和肾活检病理改变^[10];(2)尿蛋白定量通常 >3.5 g/d;(3)经本院伦理学会批准;(4)患者均签署知情同意书;(5)依从性良好者。排除标准:(1)合并精神障碍者;(2)合并其他器质性障碍如先天性心脏病者;(3)合并恶性肿瘤者;(4)对调研应用药物过敏者;(5)妊娠或哺乳期女性。

剔除标准:(1)治疗期间主动要求终止调研者;(2)治疗期

间发生严重不良事件或不良反应者;(3)治疗期间病情急剧恶化无法继续调研者。

1.2 方法

对照组接受常规西医治疗,应用药物如下:口服强的松,初始计量为 0.5 mg/kg.d,服用 8 w 后每 4 w 减 2.5~5 mg,最终保持 10 mg/d 的剂量维持治疗,同时口服他克莫司,初始计量为 0.05 mg/kg.d,治疗期间监测患者肝肾功能及血脂、血糖水平;研究组则在对照组基础上加用中药疗法,应用药物为玉屏风散合知柏地黄汤加减,具体药方如下(黄芩 20 g、白术 15 g、防风 15 g、知母 20 g、生地 20 g、山药 15 g、山茱萸 15 g、当归 15 g、川芎 15 g、茯苓 20 g、泽泻 15 g、丹皮 15 g^[11]),上述药物水煎取汁,1 剂/d,分 3 次服用。两组治疗 3 个月。

1.3 观察指标及评测标准

1.3.1 治疗有效率 于治疗 6 个月 after 评估两组治疗效果,将治疗效果区分为完全缓解、部分缓解和无效 3 类,完全缓解是指治疗后监测 24 h 尿蛋白 <0.3 g,血清白蛋白 >35 g/L;部分缓解是指治疗后 24 h 尿蛋白 ≤ 3.5 g/d 或尿蛋白下降 $>50\%$,血清白蛋白 >30 g/L,肾功能稳定;无效是指治疗后 24 h 尿蛋白 >3.5 g/d,治疗有效率=(完全缓解+部分缓解)/总例数 $\times 100\%$ ^[10]。

1.3.2 免疫指标变化 分别于治疗前及治疗后采集两组空腹静脉血 5 mL,使用离心机离心后,使用全自动生化分析仪检测两组患者治疗前后 IgA、IgG、IgM 水平。

1.3.3 尿尿生化指标 分别于治疗前后留两组空腹静脉血及尿液样本,检测其 UAER、Alb、BUN 及 Scr 等指标。

1.3.4 不良反应发生率 分别记录两组治疗期间如皮疹、肝功能损伤、多毛、牙龈增生等事件的发生率。

1.4 统计学方法

应用 SPSS 19.0,计数资料以(%)表示,采用卡方检验,计量资料以($\bar{x} \pm s$)表示,采用 t 检验, $P<0.05$ 有统计学意义。

2 结果

2.1 治疗有效率

研究组治疗有效率为 95.92 % (47/49),对照组治疗有效率为 81.63 % (40/49),两组对比有统计学意义($P<0.05$),如表 1。

表 1 治疗有效率对比[例(%)]

Table 1 Comparison of treatment efficacy[n(%)]

Groups	n	Complete remission	Partial remission	Invalid	Efficient
Study group	49	40 (81.63)	7 (14.29)	2 (4.08)	47 (95.92)*
Control group	49	36 (73.47)	4 (8.16)	9 (18.36)	40 (81.63)

Note: Compared with the control group, * $P<0.05$.

2.2 免疫指标变化情况

治疗前两组 IgA、IgG、IgM 水平对比无差异($P>0.05$),干预后两组上述指标均升高,且研究组均优于对照组($P<0.05$),如表 2。

2.3 尿尿生化指标对比

治疗前两组 UAER、Alb、BUN 及 Scr 水平对比无差异($P>0.05$),治疗后两组 UAER、BUN 及 Scr 水平均显著降低,

Alb 水平显著升高,且研究组上述指标均优于对照组($P<0.05$),如表 3。

2.4 不良反应发生率对比

研究组治疗中不良反应发生率低于对照组($P<0.05$),如表 4。

3 讨论

膜性肾病是肾病综合征常见的病因,约占我国肾活检诊断

的原发性肾炎的 10 %, 近些年发病率呈现逐年递增趋势, 患者自然预后差异大, 大约 20 %~30 % 的患者可出现自发缓解, 一部分患者表现为持续尿蛋白, 肾功能下降缓慢, 一部分患者最终进入尿毒症, 给患者个人生活及家庭带来较大的影响^[12,13]。临床研究指出, 虽然膜性肾病因较为复杂, 但其诱发该病的主要原因为感染, 有学者的研究表明, 感染约占肾病综合征反复发作病因的 76.2 %~81 %^[14], 其中上呼吸道感染占比最高, 其次为劳累、应用错误的激素等。当前西医对膜性肾病的治疗方式仍以激素或联合应用环磷酰胺为首选用药, 部分患者也可加用新一代免疫抑制剂如环孢 A 等^[15,16], 但临床实践指出, 膜性肾病患

者本身就存在血液高凝、脂质代谢紊乱和免疫力低下等症状, 长期大量应用激素会加重凝血及脂质代谢紊乱症状, 同时免疫抑制剂的应用则会进一步降低患者免疫力, 造成肾功能或肝功能损伤^[17,18], 导致患者水肿难以消退、大量蛋白尿持续存在、血浆蛋白持续下降、脂质代谢紊乱加重, 因而目前临床上倾向于寻求中西医结合的方式对膜性肾病进行治疗^[19,20]。目前越来越多的研究指出, 在应用激素、细胞毒性药物等的基础上灵活运用中医中药辩证论治, 能够取得较好的治疗效果, 尤其是对反复发作或激素抵抗性膜性肾病, 中西医结合疗法效果更为显著^[21]。

表 2 免疫指标变化情况 ($\bar{x} \pm s$)Table 2 Changes in immune indicators ($\bar{x} \pm s$)

Groups	n	IgA		IgG		IgM	
		Before intervention	After intervention	Before intervention	After intervention	Before intervention	After intervention
Study group	49	0.79 $\pm$ 0.12	1.63 $\pm$ 0.15* [#]	3.82 $\pm$ 1.36	9.21 $\pm$ 1.51* [#]	1.16 $\pm$ 0.21	1.69 $\pm$ 0.32* [#]
Control group	49	0.78 $\pm$ 0.15	0.95 $\pm$ 0.16*	3.81 $\pm$ 1.29	6.33 $\pm$ 1.22*	1.13 $\pm$ 0.16	1.51 $\pm$ 0.26*

Note: Compared with the before the same group intervention, * $P<0.05$; Compared with the control group after intervention, [#] $P<0.05$.

表 3 血尿生化指标对比 ($\bar{x} \pm s$)Table 3 Comparison of hematuria biochemical indexes ($\bar{x} \pm s$)

Groups	n	UAER (g/24 h)		Alb (g/L)		BUN (mmol/L)		Scr (μ mol/L)	
		Before intervention	After intervention	Before intervention	After intervention	Before intervention	After intervention	Before intervention	After intervention
Study group	49	4.19 $\pm$ 0.21	0.51 $\pm$ 0.06* [#]	18.68 $\pm$ 2.33	40.16 $\pm$ 2.65* [#]	16.53 $\pm$ 1.63	5.18 $\pm$ 0.62* [#]	150.16 $\pm$ 10.26	80.16 $\pm$ 6.33* [#]
Control group	49	4.22 $\pm$ 0.19	0.98 $\pm$ 0.05*	18.94 $\pm$ 2.55	30.18 $\pm$ 1.81*	16.68 $\pm$ 1.55	7.95 $\pm$ 0.55*	149.55 $\pm$ 6.98	92.53 $\pm$ 3.26*

表 4 不良反应发生率对比 [例(%)]

Table 4 Comparison of the incidence of adverse reactions to treatment [n (%)]

Groups	n	Rash	Liver function impairment	Hairy	Gingival hyperplasia	Incidence
Study group	49	1 (2.04)	1 (2.04)	0 (0.00)	0 (0.00)	2 (4.08)*
Control group	49	2 (4.08)	3 (6.12)	1 (2.04)	2 (4.08)	8 (16.33)

我们通过设立不同分组的方式, 就中西医结合疗法对膜性肾病治疗效果及机制进行了探究, 结果显示, 中西医结合治疗的研究组患者治疗有效率更高, 达到 95.92 %, 同时治疗后患者的免疫功能得到了明显的改善, IgA、IgG、IgM 水平均较治疗前有了明显的提升。现代医学研究指出, 介导膜性肾病等肾小球疾病几乎全都是免疫介导性疾病, 且多为免疫介导性炎症^[22,23], 因而临床上建议采用抗免疫和抗炎症治疗, 早在 1984 年我国即提出膜性肾病激素治疗的标准方案, 但长期应用激素存在不良反应高发的实际问题^[24,25]。祖国传统医学认为, 膜性肾病为内外因综合作用下所致, 内因多为素体亏虚、脾虚肾弱, 导致血行不畅, 或阳虚体弱, 导致血行瘀滞, 外因多为外邪入侵积于经脉, 导致脉络阻塞^[26,27]。可以发现血瘀始终贯穿于疾病始终, 因而在治疗中主张应用活血化瘀、温阳补肾的药物施治^[28]。本研究中运用的玉屏风散合知柏地黄汤加减, 其中的玉屏风散由

黄芩、白术、防风三味药材组成, 黄芩、白术具有扶正祛邪的功效, 能够提 " 正气 " 御 " 外邪 ", 防风则能够解表祛风, 三味联用具有补脾肺之气、健脾益气、强益固表的功效。知柏地黄汤源于《景岳全书》, 主要用于治疗阴虚火旺、潮热盗汗等症, 具有滋补肾阴、清利湿热的功效, 能够滋养肾阴、运气活血^[29,30]。与 Zuo 等人^[31]研究类似, 该学者通过芪苓通络方联合甲泼尼龙与环磷酰胺治疗特发性膜性肾病中高危患者, 患者的的疗效显著高于单纯的西医治疗, 同时血浆白蛋白、肾功能、血脂、纤维蛋白原等均显著改善, 且不良反应少, 说明中西医结合方案治疗特发性膜性肾病中高危患者疗效较好, 安全性更高。目前中西医结合治疗膜性肾病还没有应用到国外学者的研究中, 与本研究不同, 国外对于膜性肾病的治疗方案主要采取西药治疗^[32,33], 如磷脂酶 A2 受体、利妥昔单抗、肽GAM 免疫吸附等方法, 也取得了一定的疗效, 但是部分患者会出现药物依赖性和不良反应。

因此,本研究中将玉屏风散与知柏地黄汤联用,一方面能够增强患者免疫力、益气扶正,另一方面知柏地黄汤能够缓解患者因大量应用激素所致的阴虚阳亢及血液高凝状态,文中结果显示,研究组血尿生化指标较治疗前有了明显的缓解,也优于对照组就证实了该观点。同时不良反应发生率的对比则显示,中西医结合治疗有效降低了不良反应发生率,提示有益于长期用药和改善患者预后。

总而言之,中西医结合疗法对膜性肾病具有较好的治疗效果,能够显著改善患者免疫功能及肝功能,同时还能够降低治疗中不良反应发生率,值得进行临床推广。本研究也存在一定的不足,样本量少,没有进行后续的远期观察,同时没有对中西药结合治疗膜性肾病的机制深入的研究,后期需要深入的研究治疗的具体机制,寻找治疗的靶点,为临床治疗提供新的方案。

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