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他克莫司联合黄葵胶囊治疗难治性膜性肾病的临床疗效

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摘要 目的：探讨他克莫司联合黄葵胶囊治疗难治性膜性肾病疗效及安全性。**方法**：选取 2014 年 3 月 -2015 年 10 月我院收治的 60 例难治性膜性肾病患者，按随机数字表法分为观察组和对照组各 30 例，对照组给予泼尼松治疗，观察组在此基础上增加他克莫司联合黄葵胶囊口服，两组均治疗 6 个月，观察两组临床疗效，检测并对比两组治疗前后尿蛋白（uPRO）、血清白蛋白（sALB）、血清肌酐（sCr）、血谷丙转氨酶（sALT）、肿瘤坏死因子 α（TNF-α）、转化生长因子 β1（TGF-β1）以及不良反应情况。**结果**：观察组的有效率高于对照组（P<0.05）；治疗后两组 uPRO、TNF-α、TGF-β1 均明显降低，sALB、sCr 明显升高（P<0.05），且观察组 uPRO、TNF-α、TGF-β1 低于对照组（P<0.05）；两组不良反应发生率比较差异无统计学意义（P>0.05）。**结论**：他克莫司联合黄葵胶囊治疗难治性膜性肾病具有较好的疗效，降低肾功能损伤，不良反应低，值得临床推广。

关键词：他克莫司；黄葵胶囊；膜性肾病；难治性

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Clinical Effects of Tacrolimus Combined with Okra Capsule in Treatment of Refractory Membranous Nephropathy

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ABSTRACT Objective: To investigate the effect and safety of tacrolimus combined with Okra capsule in treatment of the refractory membranous nephropathy. **Methods:** Selected 60 patients with refractory membranous nephropathy who were treated in our hospital from March 2014 to October 2015, and they were divided into observation group and control group with 30 cases in each group according to the random number table method. The control group was treated with prednisone, and the observation group was treated with tacrolimus combined with Okra capsule on the basis of the control group, the courses of treatment were 6 months in two groups. The clinical effects were observed in two groups, the levels of urine protein (uPRO), serum Albumin (sALB), serum Creatinine (sCr), serum Alanine amino-transferase (sALT), tumor necrosis factor-α (TNF-α) and transforming growth factor-β1(TGF-β1) were detected and compared in two groups before and after treatment, and the adverse reactions were recorded in two groups. **Results:** The total effective rate of the ob- servation group was significantly higher than control group (P<0.05). Compared with before treatment, the levels of uPRO, TNF-α,TGF-β1 in two groups were decreased after treatment, while sALB, sCr were increased (P<0.05), and uPRO, TNF-α,TGF-β1 in the observation group were lower than the control group (P<0.05). There was no significant difference in the incidence of adverse reactions between the two groups (P>0.05). **Conclusion:** Tacrolimus combined with Huangkui capsule in the treatment of refractory membranous nephropathy has good curative effect, reduce renal damage, and low adverse reaction, worthy of promotion.

Key words: Tacrolimus; Okra capsules; Membranous nephropathy; Refractory

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前言

膜性肾病是引起成人肾病综合征的最主要病理类型，以大量的蛋白尿为临床表现[1]，病理以肾小球基底膜的上皮细胞形成免疫复合物为主的一组疾病。难治性膜性肾病是膜性肾病较难治疗的一种，目前临床中尚未有统一的治疗方案，大多采用免疫抑制疗法联合激素的方式进行治疗[2]。常用的免疫抑制剂包含他克莫司、环孢素等，但存在复发的风险，部分患者甚至出现耐药，因此临床应用受到限制[3]。近年来，中药因其疗效肯定，且产生副作用小，在国内肾病学界已形成了中西医结合是治疗膜性肾病一种较为满意治疗方法的共识[4]。黄葵胶囊具有清利湿热，解毒消肿的功效，作为治疗难治性膜性肾病的中成药，具有较好的疗效[5]。由此，本研究探讨他克莫司联合黄葵胶囊治疗难治性膜性肾病的疗效和安全性，旨在为临床治疗提供数据参考，现报道如下。

1 资料与方法

1.1 临床资料

将 2014 年 3 月 -2015 年 10 月在我院住院治疗的 60 例难

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治性膜性肾病患者纳入本次研究，纳入标准：(1)临床表现符合肾病综合征[6]，即尿蛋白(Urine Protein，uPRO)>3.5 g/d，血清白蛋白(Serum Albumin，sALB)<30 g/L，血清肌酐(Serum Creatinine，sCr)<133 μmol/L，水肿，血脂升高；(2)属难治性肾病[7]，即激素依赖，激素抵抗，激素不耐受，反复发作；(3)肾穿刺活检病理类型符合膜性肾病，并且排除继发于肿瘤、药物、感染、自身免疫性疾病等继发性肾病综合征。采用随机数字表法将 60 例患者分为对照组和观察组。其中对照组 30 例，男性 19 例，女性 11 例；年龄范围 20-80 岁，平均年龄(53.81± 13.37)岁；病程 38-65 月，平均病程(43.27± 14.18)月；组织学评分Ⅱ、Ⅲ期分别有 14 和 16 例；而观察组有 30 例，男性 16 例，女 14 例；年龄范围 20-79 岁，平均年龄(54.61 ± 11.25)岁；病程 35-68 月，平均病程(44.29± 12.38)月；组织学评分Ⅱ、Ⅲ期分别有 12 和 18 例，两组患者性别比例等一般资料经比较后无统计学差异(P>0.05)，所以存在可比性。患者或家属均签署知情同意书。

1.2 治疗方法

根据两组患者情况，常规服用他汀类药物降血脂、抗凝剂及利尿剂等药物，此外，观察组采用他克莫司＋黄葵胶囊＋泼尼松片联合治疗：他克莫司(国药集团川抗制药有限公司生产，批号：J20140148)设定剂量为 0.05 mg/(kg·d)，分为饭前 1 h 和饭后 2 h 服用；联合黄葵胶囊 (江苏苏中药业公司生产，0.5 g/粒，批号：Z19990040)，每次 3 粒，每日 3 次；泼尼松片：按 0.4 mg/(kg·d)口服。对照组仅采用泼尼松片治疗，其用法用量同观察组。两组患者均观察治疗半年时间。

1.3 观察指标

测定两组患者治疗前后的 uPRO、sALB、sCr、血谷丙转氨酶 (Serum Alanine aminotransferase，sALT)、肿瘤坏死因子 α (Tumor Necrosis Factor α，TNF-α)、转化生长因子 β1(Transforming Growth Factor-β，TGF-β1)水平。收集治疗前后所有患者的清晨空腹静脉血 5 mL 及 24 h 尿液，静脉血静置后，置于离心机内以 3000 rpm 离心 15 min，上层乳黄色液体即为血清，及时送检。所有标本的 uPRO、sALB、sCr、sALT、TNF-α、TGF-β1 检测，均使用本院检验科 Olympus AU5400 全自动血尿生化分析仪，uPRO、sALB 的检测方法为比浊法，试剂盒购自西班牙 biosysterms 公司，sCr、sALT、TNF-α、TGF-β1 的检测方法为酶法，试剂盒购自日本关东化学公司，校准液均使用试剂配套的标准。对患者在治疗过程中发生的不良反应情况(肝、肾功能损害以及血液系统损害、感染、胃肠道反应等)进行记录并对比。

1.4 疗效判定标准[3]

完全缓解：多次测定 uPRO 为阴性，且 uPRO<0.2 g/d，sALB 水平正常；显著缓解：多次测定 uPRO<1 g/d，sALB 水平明显改善；部分缓解：多次测定 uPRO<3.5 g/d，sALB 水平有所改善；无效：uPRO 及 sALB 水平无任何改善或恶化。总有效率＝(完全缓解例数＋显著缓解例数＋部分缓解例数)/ 总例数×100%。

1.5 统计学方法

本研究数据使用 SPSS16.0 软件进行处理，两组患者的计数资料由 n 或%表示，组间比较行 x^2 检验，两组患者的计量资料由($\bar{x}$± s)表示，经由 t 检验比较组内和组间数据，检验标准为 α=0.05。

2 结果

2.1 两组患者临床疗效比较

观察组总有效率为 93.33%，明显高于对照组的 70.00%，差异有统计意义(x^2=5.454，P=0.020)，详细见表 1。

表 1 两组患者临床疗效比较[n(%)]

Table 1 Comparison of clinical effects between two groups [n (%)]

Groups	n	Complete remission	Significant remission	Partial remission	Invalid	Total effective
Control group	30	8(26.67)	10(33.33)	3(10.00)	9(30.00)	21(70.00)
Observation group	30	13(43.33)	9(30.00)	6(20.00)	2(6.67)	28(93.33)

2.2 两组患者治疗前后各项临床指标对比

两组患者治疗前的 uPRO、sALB、sCr、sALT、TNF-α、TGF-β1 水平经比较均无统计学差异(P>0.05)。治疗后两组的 uPRO、TNF-α、TGF-β1 均有明显降低，sALB、sCr 明显升高(P<0.05)，且观察组 uPRO、TNF-α、TGF-β1 明显低于对照组(P<0.05)。两组患者治疗后的 sALB、sCr、sALT 经比较无统计学差异(P>0.05)，见表 2。

表 2 两组患者治疗前后各项临床指标对比

Table 2 Comparison of the clinical indexes of the two groups before and after treatment

Groups	Time	uPRO(g/d)	sALB(g/L)	sCr(mmol/L)	sALT(U/L)	TNF-α(g/L)	TGF-β1(μg/L)
Control group	Before treatment	5.87± 2.13	28.37± 4.86	77.34± 22.59	26.73± 7.02	3.42± 0.95	93.83± 8.56
	After treatment	1.56± 1.03*	37.43± 3.95*	85.44± 22.79*	30.10± 6.21	2.26± 1.02*	54.32± 9.58*
Observation group	Before treatment	5.66± 2.08	28.52± 4.78	78.02± 21.32	27.07± 5.82	3.58± 1.06	96.86± 9.14
	After treatment	0.57± 0.82*△	37.69± 3.74*	90.45± 20.75*	30.32± 5.49	1.64± 1.27*△	31.43± 11.34*△

Note: Compared with before treatment, *P<0.05; Compared with the control group after treatment, △ P<0.05.

2.3 不良反应

观察组患者发生不良反应情况：胃肠道反应和上呼吸道感

染各 1 例,不良反应发生率为 6.67%，经对症治疗后症状好转,未终止治疗。而对照组共有 3 例(10.00%)发生不良反应,其中 2 例为肺部感染,出现 1 例为胃肠道反应,经对症治疗后好转。两组间的不良反应发生率经比较无统计学差异(x^2=0.218,P=0.640),且两组患者均未发现有血白细胞下降、肝功能异常及血压水平升高或降低。

3 讨论

在我国有 80%左右膜性肾病患者具有肾病综合征的表现,其中原发性肾病综合征患者中难治性肾病综合征的占比高达 50-60 %[8]。目前对于难治性膜性肾病仍没有较为满意的治疗方案，例如在膜性肾病的治疗中常见的药物有采用糖皮质激素,糖皮质激素和细胞毒药物导致感染发生等影响患者最终生存率的研究结果也屡有报道。膜性肾病治疗方案一直是困扰临床医疗工作者的难题[9],因此,在结合中西医药方面寻求有效的治疗方案成为肾脏病学者的研究热点方向。他克莫司是作为新型的免疫抑制剂,属 23 元大环内酯类的抗生素,作用机制是主要通过干扰依赖性的信号传导途径,去抑制活化细胞核因子的去磷酸化,再而导致转录想要基因阻遏,最终以达到免疫抑制剂作用[10]。他克莫司能有效抑制 T 细胞的活化和增生,且不良反应少,因此国内外不少关于他克莫司治疗难治性膜性肾病的研究报告[9,11]。黄葵为中医中常用药物,味甘、性寒、无毒。经黄葵提取而成的黄葵胶囊中主要包含了以下几种有效成分:槲皮素-3 - 杨槐爽糖苷、金丝桃苷、槲皮素、杨梅黄素以及槲皮素 -3 - 葡萄糖苷,可以有效的改善肾小球免疫炎症反应,减少循环系统中免疫复合物的产生,抑制血小板的聚集,降低对肾功能的损害等作用[12,13]。研究显示,黄葵胶囊可有效的清除氧自由基,降低尿蛋白水平,提高血清蛋白含量[14]。

本次研究探讨了他克莫司联合黄葵胶囊治疗难治性膜性肾病的疗效,结果显示,经过半年临床疗效观察,结果发现观察组总有效率为 93.33%,明显高于对照组的 70.00%,提示他克莫司联合黄葵胶囊具有较高的疗效。他克莫司作为免疫抑制剂,加上黄葵的抗炎、清除免疫复合物的作用,对因治疗了膜性肾病,故观察组的疗效显著高于对照组。uPRO 是肾功能损害的最直接指标,TNF-α 是机体炎症及免疫反应的调节因子,TGF-β1 是目前已知的促进肾脏疾病进展的主要细胞因子,是目前公认的肾纤维化指标 [15,16]。本研究结果显示，治疗后两组 uPRO、TNF-α、TGF-β1 均有显著下降,且观察组显著低于对照组。说明他克莫司联合黄葵胶囊通过降低肾功能损伤、改善炎症应激反应及肾纤维化情况对难治性膜性肾病发挥作用。这与他克莫司抑制 T 细胞的活化和增殖,抵抗炎症,同时黄葵胶囊有效地清除氧自由基,降低尿蛋白有关[17,18]。另外,本研究观察组与对照组之间的不良反应发生率不存在差异,说明他克莫司联合黄葵胶囊后不会增加治疗的安全风险,具有较好的安全性。研究是小样本量的临床研究,治疗仅观察半年,存在一定局限性。据文献报道显示，短疗程他克莫司治疗后可能发生患者的复发[19,20];虽然本研究期间尚未发现有复发患者,但是进一步情况目前尚未清楚。

综上所述,他克莫司联合黄葵胶囊能显著提高难治性膜性肾病临床有效率,其作用机制可能与降低肾功能损伤、改善炎症应激反应及肾纤维化情况有关,且呈现副作用小。但是仍需多中心、大样本量、前瞻性的随机对照研究来进一步加以验证。

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