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黄芪颗粒剂联合厄贝沙坦对 IgA 肾病患者肾功能、炎性因子及免疫功能的影响 *

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摘要 目的：探讨黄芪颗粒剂联合厄贝沙坦对 IgA 肾病（IgAN）患者肾功能、炎性因子及免疫功能的影响。**方法：**回顾性分析 2016 年 3 月 ~2019 年 8 月期间于我院就诊的 98 例 IgAN 患者的临床资料，根据用药方案的不同将患者分为对照组（n=49）和治疗组（n=49），对照组予以厄贝沙坦治疗，治疗组在对照组的基础上联合黄芪颗粒剂治疗，比较两组患者疗效、肾功能、炎性因子及免疫功能，记录两组治疗期间不良反应情况。**结果：**治疗组治疗 2 个月后的临床总有效率为 91.84%（45/49），高于对照组的 73.47%（36/49）（*P*<0.05）。治疗 2 个月后，两组白细胞介素 -6（IL-6）、超敏 C- 反应蛋白（hs-CRP）、肿瘤坏死因子 -α（TNF-α）均较治疗前下降，且治疗组低于对照组（*P*<0.05）。两组不良反应发生率比较无差异（*P*>0.05）。治疗 2 个月后，两组 24 h 尿蛋白定量（24h-Upro）、血肌酐（Scr）、尿素氮（BUN）均较治疗前下降，且治疗组低于对照组（*P*<0.05）。治疗 2 个月后，两组 $CD4^+/CD8^+$、$CD4^+$ 较治疗前下降，且治疗组低于对照组（*P*<0.05）；$CD8^+$ 较治疗前升高，且治疗组高于对照组（*P*<0.05）。**结论：**黄芪颗粒剂联合厄贝沙坦治疗 IgAN 患者，疗效确切，可有效改善患者肾功能、免疫功能，降低炎性因子水平，且安全可靠。

关键词：黄芪颗粒剂；厄贝沙坦；IgA 肾病；肾功能；炎性因子；免疫功能

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Effect of Astragalus Granule Combined with Irbesartan on Renal Function, Inflammatory Factors and Immune Function in IgA Nephropathy*

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ABSTRACT Objective: To investigate the effect of Astragalus granule combined with irbesartan on renal function, inflammatory factors and immune function in patients with IgA nephropathy (IgAN). **Methods:** The clinical data of 98 patients with IgAN from March 2016 to August 2019 were analyzed retrospectively, the patients were divided into control group (n=49) and treatment group (n=49) according to different medication plans. The control group was treated with irbesartan. The treatment group was treated with Astragalus granule on the basis of the control group. The curative effect, renal function, inflammatory factor and immune function of the two groups were compared. Adverse reactions during treatment in both groups were recorded. **Results:** The total effective rate of the treatment group at 2 months after treatment was 91.84% (45/49), which was higher than 73.47% (36/49) of the control group (*P*<0.05). 2 months after treatment, the levels of high sensitive interleukin-6(IL-6), C-reactive protein (hs-CRP), tumor necrosis factor-α(TNF-α) of the two groups were lower than those before treatment, those of the treatment group were lower than those of the control group (*P*<0.05). There was no significant difference in the incidence of adverse reactions between the two groups (*P*>0.05). 2 months after treatment, 24h urine protein quantity (24h-Upro), blood creatinine (Scr) and urea nitrogen (BUN) of the two groups were lower than those before treatment, and the treatment group was lower than the control group(*P*<0.05). 2 months after treatment, $CD4^+/CD8^+$, $CD4^+$ of the two groups decreased compared with those before treatment, and the treatment group was lower than the control group (*P*<0.05). $CD8^+$ was higher than that before treatment, and the treatment group was higher than the control group (*P*<0.05). **Conclusion:** Astragalus granule combined with irbesartan in the treatment of patients with IgAN, the effect is accurate, which can effectively improve the renal function, immune function, reduce the level of inflammatory factors, and it is safe and reliable.

Key words: Astragalus granule; Irbesartan; Immunoglobulin A nephropathy; Renal function; Inflammatory factor; Immune function

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前言

IgA 肾病(IgAN)是指免疫球蛋白 A(IgA)为主的免疫球蛋白在毛细血管处以及肾小球系膜区沉积引发的一系列临床症状,表现为不同程度的血尿、蛋白尿、高血压和肾功能损害,危害患者生命健康安全[1-3]。现临床针对 IgAN 的治疗尚无统一方案,多以血管紧张素转化酶抑制剂或者血管紧张素 II 受体拮抗剂为主 [4,5]。厄贝沙坦是血管紧张素 II 受体拮抗剂的代表类药物,其在高血压等疾病中的疗效已得到证实[6]。既往研究证实厄贝沙坦具有减少蛋白尿和阻止肾脏疾病进展的作用[7]。而黄芪颗粒剂为中药颗粒剂型,具有补气固表、利尿的功效[8]。现临床有关厄贝沙坦联合黄芪颗粒剂治疗对 IgAN 患者炎性因子、肾功能及免疫功能的综合性报道研究尚不多见,本研究就此展开分析,以期为临床 IgAN 的治疗提供参考。

1 资料与方法

1.1 一般资料

采用回顾性研究方法，筛选并分析 2016 年 3 月 ~2019 年 8 月期间于我院就诊的 98 例 IgAN 患者的临床资料。纳入标准:均符合诊断标准《肾脏内科学》[9],并通过肾穿刺活检确诊;排除标准:合并精神疾患、认知功能障碍、心肝肺等重要脏器功能障碍者、继发性肾小球肾炎者、合并免疫缺陷或恶性肿瘤者、妊娠或哺乳期妇女。根据用药方案的不同将患者分为对照组(n=49,厄贝沙坦治疗)和治疗组(n=49,厄贝沙坦联合黄芪颗粒剂治疗),其中对照组男 28 例,女 21 例,年龄 41~69 岁,平均(52.81± 4.16)岁;病程 1~7 年,平均(3.62± 0.87)年;病理类型:系膜增生型 20 例,局灶增生型 17 例,肾小球硬化型 12 例。治疗组男 30 例,女 19 例,年龄 39~70 岁,平均(52.97± 3.88)岁;病程 1~9 年,平均(3.71± 0.92)年;病理类型:系膜增生型 19 例,局灶增生型 19 例,肾小球硬化型 11 例。两组一般资料对比无统计学差异(P>0.05),具有可比性。

1.2 方法

均予以降低血压、平衡电解质、利尿、适当休息、优质高热量中等蛋白饮食,在此基础上,对照组予以厄贝沙坦(国药准字 H20058709,浙江华海药业股份有限公司,规格:厄贝沙坦 150 mg/ 氢氯噻嗪 12.5 mg)治疗,150 mg/ 次,1 次 /d,口服。治疗组在对照组的基础上联合黄芪颗粒剂(江阴天江药业有限公司,规格:每袋装 1.5 g,相当于饮片 10 g)治疗,温水冲服,1 袋 / 次,2 次 /d,口服。均治疗 2 个月。

1.3 观察指标

1.3.1 疗效 统计两组总有效率。总有效率 = 显效率 + 治愈率 + 有效率[10]。治愈:肾功能恢复正常,多次测定蛋白尿呈阴性,24h-Upro<0.2 g;显效:肾功能接近正常,临床症状基本消失,多次检测 24h-Upro<1 g;有效:24h-Upro<3 g,肾功能有所好转;无效:临床症状依然存在,肾功能未见变化,24h-Upro 未见减少甚至增加。

1.3.2 血清指标 抽取两组患者治疗前、治疗 2 个月后的清晨空腹静脉血 9 mL，分为三管，一管经日本 OLYMPUS-AU600 型全自动生化分析仪检测肾功能指标:24h-Upro、血肌酐(Scr)、尿素氮(BUN)。一管经美国 BD 公司生产的 Fascalibur 流式细胞仪检测 T 淋巴细胞亚群指标:$CD4^+$、$CD8^+$ 与 $CD4^+/CD8^+$。最后一管经常规离心处理(3500 r/min 的转速,12 cm 的离心半径,离心 15min),分离上清待测,置于冰箱中保存备用,参考试剂盒(上海化工生物工程有限公司)说明书步骤,采用酶联免疫吸附法检测炎性因子指标：白细胞介素 -6(IL-6)、超敏 C- 反应蛋白(hs-CRP)、肿瘤坏死因子 -α(TNF-α)。

1.3.3 安全性评价 观察两组不良反应情况。

1.4 统计学方法

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

2 结果

2.1 疗效比较

治疗 2 个月后,治疗组的临床总有效率为 91.84%(45/49),高于对照组的 73.47%(36/49)(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	Valid	Invalid	Total effective rate
Control group(n=49)	6(12.24)	12(24.49)	18(36.73)	13(26.53)	36(73.47)
Treatment group(n=49)	10(20.41)	16(32.65)	19(38.78)	4(8.16)	45(91.84)
x^2					5.765
P					0.016

2.2 炎性因子比较

治疗前，两组 hs-CRP、IL-6、TNF-α 比较无差异(P>0.05);治疗 2 个月后,两组 hs-CRP、IL-6、TNF-α 均下降,且治疗组较对照组低(P<0.05);详见表 2。

2.3 肾功能指标比较

治疗前，两组 24h-Upro、Scr、BUN 比较无差异(P>0.05);治疗 2 个月后，两组 24h-Upro、Scr、BUN 均较治疗前下降,且治疗组较对照组低(P<0.05);详见表 3。

2.4 免疫功能指标比较

治疗前,两组 $CD4^+$、$CD8^+$ 与 $CD4^+/CD8^+$ 比较无差异(P>0.05);治疗 2 个月后,两组 $CD8^+$ 较治疗前升高,且治疗组较对照组高(P<0.05);$CD4^+/CD8^+$、$CD4^+$ 较治疗前下降,且治疗组较对照组低(P<0.05);详见表 4。

表 2 炎性因子水平比较($\bar{x}\pm s$)

Table 2 Comparison of inflammatory factors ($\bar{x}\pm s$)

Groups	hs-CRP(mg/L)		IL-6(pg/mL)		TNF-α(ng/mL)	
	Before treatment	2 months after treatment	Before treatment	2 months after treatment	Before treatment	2 months after treatment
Control group(n=49)	9.78± 0.37	6.42± 0.33*	143.56± 18.39	92.36± 15.32*	4.88± 0.27	3.64± 0.29*
Treatment group(n=49)	9.72± 0.48	4.16± 0.41*	142.61± 20.35	73.39± 14.35*	4.94± 0.39	2.87± 0.18*
t	0.693	30.058	0.242	6.326	0.885	15.792
P	0.490	0.000	0.809	0.000	0.378	0.000

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

表 3 肾功能指标比较($\bar{x}\pm s$)

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

Groups	24h-Upro(g)		Scr(μmol/L)		BUN(mmol/L)	
	Before treatment	2 months after treatment	Before treatment	2 months after treatment	Before treatment	2 months after treatment
Control group(n=49)	2.49± 0.27	1.52± 0.21*	141.39± 23.47	91.64± 12.11*	10.33± 1.27	7.71± 1.04*
Treatment group(n=49)	2.53± 0.32	0.83± 0.17*	142.06± 24.27	75.03± 11.58*	10.72± 1.05	4.23± 0.96*
t	0.669	17.877	0.139	6.939	1.657	17.211
P	0.505	0.000	0.890	0.000	0.101	0.000

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

表 4 免疫功能指标比较($\bar{x}\pm s$)

Table 4 Comparison of immune function indexes($\bar{x}\pm s$)

Groups	$CD4^+$(%)		$CD8^+$(%)		$CD4^+/CD8^+$	
	Before treatment	2 months after treatment	Before treatment	2 months after treatment	Before treatment	2 months after treatment
Control group(n=49)	58.27± 5.52	53.49± 4.62*	26.76± 3.23	30.53± 3.17*	2.18± 0.19	1.75± 0.24*
Treatment group(n=49)	58.43± 4.16	45.87± 5.03*	26.82± 3.15	34.94± 3.11*	2.18± 0.22	1.31± 0.16*
t	0.162	4.489	0.093	6.605	0.267	15.861
P	0.872	0.000	0.926	0.000	0.790	0.000

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

2.5 不良反应发生率比较

两组不良反应发生率比较差异无统计学意义(P>0.05)。见表 5。

表 5 不良反应发生率比较[例(%)]

Table 5 Comparison of adverse reactions[n(%)]

Groups	Nausea and vomiting	Gastrointestinal discomfort	Rash	Total incidence
Control group(n=49)	2(4.08)	1(2.04)	2(4.08)	5(10.20)
Treatment group(n=49)	2(4.08)	3(6.12)	1(2.04)	6(12.24)
x^2				0.102
P				0.749

3 讨论

IgAN 是目前世界范围内最常见的原发性肾小球疾病，会对肾功能造成较大的损害，在患者确诊 10~20 年后可发展为终末期肾脏疾病，危及患者性命[11-13]。IgAN 的主要病理基础为 IgA 在肾小球系膜区呈现弥漫或全球沉积，且存在基质增多，系膜细胞增生等情况[14,15]。现临床针对 IgAN 的具体发病机制尚不十分明确，多认为其病情发生发展与机体免疫失衡、炎症反应

过度激活等多种因素有关[16]。既往也有研究显示[17],IgAN 患者存在 T 细胞亚群紊乱情况,主要表现为 Th2 细胞增多以及 Thl 细胞减少。同时也有研究报道证实[18],慢性肾病患者血清微炎症状态与肾功能呈负相关。IgAN 患者体内抗原与抗体发生免疫反应,肾功能受损,肾组织旁分泌或自分泌多种炎症因子,而这些炎症因子又可反作用于肾小球系膜细胞, 加重肾损伤[19]。因此,临床治疗 IgAN 在改善症状,阻止疾病进展的同时,还应尽可能的调节机体免疫功能,抑制炎症反应过度激活。现临床常用的西医治疗 IgAN 的药物如厄贝沙坦,通过控制机体蛋白尿而改善肾小球 " 三高 " 状态(高滤过、高压力和高灌注),从而缓解患者临床症状。然而 IgAN 患者蛋白尿严重程度不一,针对蛋白尿较多者,若无限制加大厄贝沙坦的剂量往往易并发低血压、肾功能损害、高血钾等不良反应,效果欠佳[20-22]。故寻找适当的药物联合厄贝沙坦治疗 IgAN 患者,对于改善患者疗效具有积极的临床意义。

祖国医学认为,IgAN 属 " 虚劳 "" 关格 " 范畴,主要病理改变为 " 脾肾两虚、热、湿、毒内蕴 ",治则应以清利湿热、清热解毒为主[23]。黄芪颗粒剂是由黄芪制成的单方制剂,现代药理研究证实黄芪颗粒剂对体液免疫、非特异性免疫、细胞免疫均有明显调节作用,可增强肾血流量[24]。有研究称中西医结合治疗 IgAN 患者具有增效减毒的特点,可弥补西药不良反应多、耐药增加等不足[25]。故本研究设置对照组,在厄贝沙坦治疗 IgAN 患者的基础上联合黄芪颗粒剂治疗,结果显示治疗组肾功能改善效果优于对照组,疗效高于对照组,可见中西医结合治疗方案效果显著,可进一步提高治疗效果,改善患者肾功能。两种药物联合应用可协同性的降低尿蛋白,发挥调节免疫,改善机体肾脏功能以及炎性状态的作用。本次研究结果还显示,黄芪颗粒剂联合厄贝沙坦治疗 IgAN 患者, 可有效改善患者免疫功能,降低炎性因子水平。其中 IL-6 可诱导肾小球膜细胞炎性生长,TNF-α 是机体炎症反应、免疫反应重要的调节因子,hs-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[26-28]。而以往的研究表明[29],IgAN 患者的免疫功能紊乱,主要体现为 $CD4^+/CD8^+$ 水平偏高。本研究中治疗组 $CD4^+$、$CD8^+$、$CD4^+/CD8^+$ 改善均优于对照组, 这主要是因为黄芪颗粒剂可有效减轻肾小球系膜细胞、基质增生,减少免疫复合物的沉积,进而有效改善患者血尿、蛋白尿症状,调节 T 淋巴细胞亚群平衡,减轻炎性组织浸润[30]。另通过分析两组不良反应发生率可知,两种治疗方案均安全可靠,不良反应较为轻微,患者可耐受。

综上所述, 黄芪颗粒剂联合厄贝沙坦治疗 IgAN 患者,可有效改善患者肾功能、免疫功能,降低炎性因子水平,且安全可靠,疗效确切。

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