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泼尼松联合来氟米特治疗 IgA 肾病的临床疗效 及对患者血清 VEGF 及 MMP-9 水平的影响

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摘要 目的: 探讨泼尼松联合来氟米特治疗 IgA 肾病的临床疗效及对患者血清内皮生长因子 (vascular endothelial growth factor, VEGF) 及基质金属蛋白酶-9 (matrix metalloproteinase -9, MMP-9) 水平的影响。**方法:** 选择我院肾病内科收治的 IgA 肾病患者 60 例, 随机分为对照组与观察组, 每组各 30 例。对照组患者给予泼尼松治疗, 观察组在对照组基础上给予来氟米特治疗。比较两组患者治疗后的临床疗效及不良反应发生情况; 分别于治疗前后检测和比较两组患者的肾功能、血清 VEGF 及 MMP-9 水平。**结果:** 治疗后, 对照组患者临床总有效率为 73.33 %, 总不良反应率为 10.00 %; 观察组患者临床总有效率为 86.67 %, 明显高于对照组, 而总不良反应率为 3.33 %, 显著低于对照组 ($P < 0.05$)。治疗后, 两组患者血清血尿素氮 (blood urine nitrogen, BUN)、血肌酐 (creatinine, Cr)、VEGF 及 MMP-9 水平均明显低于本组治疗前, 肾小球滤过率 (glomerular filtration rate, GFR) 水平明显高于本组治疗前; 且观察组患者治疗后血清 BUN、Cr、VEGF 及 MMP-9 水平明显低于对照组, GFR 水平明显高于对照组 ($P < 0.05$)。**结论:** 泼尼松联合来氟米特治疗 IgA 肾病的临床疗效明显优于单用泼尼松治疗, 可更显著改善患者肾脏功能, 可能与其降低患者血清 VEGF 及 MMP-9 水平有关。

关键词: 泼尼松; 来氟米特; IgA 肾病; 肾功能; 内皮生长因子; 基质金属蛋白酶-9

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Clinical Efficacy of Prednisone combined with Leflunomide in the Treatment of Patients with IgA Nephropathy and Its Effect on the Serum VEGF and MMP-9 Levels

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ABSTRACT Objective: To investigate the effects of prednisone combined with leflunomide on the curative effect, renal function, VEGF and MMP-9 levels in patients with IgA nephropathy. **Methods:** 60 patients with IgA nephropathy admitted in our hospital were randomly divided into the control group and the observation group, 30 cases in each group. The patients in control group were treated with prednisone, and the patients in observation group were given leflunomide on the basis of control group. The clinical efficacy and incidence of adverse reactions were compared between the two groups after treatment. The renal function, serum VEGF and MMP-9 levels of the two groups were measured and compared before and after treatment. **Results:** After treatment, the total clinical effective rate of control group was 73.33 % and the total adverse reaction rate was 10.00 %. The total clinical effective rate of observation group was 86.67 %, which was higher than that of the control group, and the total adverse reaction rate was 3.33 %, which was lower than that of the control group ($P < 0.05$). After treatment, the levels of serum BUN, Cr, VEGF and MMP-9 in both groups were significantly lower than those before treatment, and the level of GFR was significantly higher than that before treatment. The levels of serum BUN, Cr, VEGF and MMP-9 of observation group were significantly lower than that of the control group. The level of GFR was significantly higher than that of the control group ($P < 0.05$). **Conclusion:** The clinical effect of prednisone combined with leflunomide in the treatment of IgA nephropathy is obviously better than that of prednisone alone. It can more significantly improve the renal function of patients, which may be related to the reduction of serum VEGF and MMP-9 levels of patients.

Key words: Prednisone; Leflunomide; IgA nephropathy; Renal function; VEGF; MMP-9

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前言

IgA 肾病是临床常见的原发性肾小球疾病, 是指以 IgA 为主的免疫球蛋白在肾小球系膜区沉积的原发性肾小球病^[1-3]。临

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床表现为反复发作性肉眼血尿或镜下血尿,可伴有不同程度蛋白尿,部分患者可以出现水肿、严重高血压或者肾功能不全等,严重影响患者生活质量^[4-6]。

泼尼松属于糖皮质激素类药物,可促进蛋白质分解转变为糖,减少葡萄糖的利用^[7-9]。保护 IgA 肾病患者肾功能^[10]。研究表明尼泼松与免疫抑制剂合用,效果更佳^[11]。来氟米特为具有抗增殖活性的异噻唑类衍生物,是一种新型免疫抑制剂,可用于治疗慢性肾炎及其他肾脏疾病等^[12-14]。本研究主要观察了泼尼松联合来氟米特治疗 IgA 肾病患者临床疗效及对患者肾功能及血清 VEGF 及 MMP-9 水平的影响,以期为 IgA 肾病的治疗提供更多临床依据,现报道如下。

1 资料与方法

1.1 一般资料

选取 2014 年 1 月~2017 年 8 月我院肾病内科接收的 IgA 肾病患者 60 例。诊断标准:所有患者均符合《肾脏病学》^[15]中关于 IgA 肾病的诊断标准。入选患者随机分为对照组与观察组。对照组 30 例,男 18 例,女 12 例,年龄 20~58 岁,平均年龄(41.8±4.2)岁,局灶增生坏死性 IgA 肾病 6 例,局灶增生硬化性 IgA 肾病 6 例,局灶在增生性 IgA 肾病 10 例,轻度系膜增生性 IgA 肾病 8 例,LEE 分级^[16]:Ⅱ级 8 例,Ⅲ级 16 例,Ⅳ级 6 例;观察组 30 例,男 16 例,女 14 例,年龄 29~58 岁,平均年龄(42.9±4.5)岁,局灶增生坏死性 IgA 肾病 5 例,局灶增生硬化性 IgA 肾病 7 例,局灶在增生性 IgA 肾病 11 例,轻度系膜增生性 IgA 肾病 7 例,LEE 分级^[16]:Ⅱ级 7 例,Ⅲ级 16 例,Ⅳ级 7 例;入选标准:①符合 IgA 肾病诊断标准且肾穿刺活检病理证实为 IgA 肾病患者;②血肌酐<150 μmol·L⁻¹;③24 h 尿蛋白定量≥1.0 g。排除标准:①6 个月内曾使用免疫抑制药者;②对本研究所用药物过敏者;③合并紫癜性肾炎等严重肾病患者;④妊娠期妇女。此次研究已获得本院伦理委员会批准,患者均签署知情同意书。两组患者的一般资料比较差异均无统计学意义($P>0.05$),具有可比性。

1.2 方法

入选患者均给予常规治疗:给予血管紧张素转化酶抑制药

(angiotensin converting enzyme inhibitor, ACEI)或血管紧张素受体阻断药(angiotensin receptor blocker, ARB)或联合钙通道阻滞药、利尿药等降压药物控制血压。对照组患者在常规治疗基础上给予醋酸泼尼松(浙江仙琚制药股份有限公司,国药准字(H33021207)治疗:口服,1.0 mg/kg, qd, 6 周后逐渐减量,至 12 周时降至 0.5 mg/kg。观察组在对照组治疗基础上给予来氟米特(苏州长征-欣凯制药有限公司,国药准字 H20000550)治疗:口服,50 mg, qd, 3d 后降至 20 mg。两组患者均治疗 3 个月。

1.3 疗效观察

观察两组患者治疗后临床疗效,并记录不良反应发生情况。显效:患者 24 h 尿蛋白定量下降≥50%,血肌酐下降≥20%;有效:患者 24 h 尿蛋白定量下降 30%~50%,血肌酐无明显变化或增减<20%;无效:未达到上述标准。总有效率=(显效例数+有效例数)/总例数×100%。

1.4 肾功能检测

分别于治疗前后取两组患者静脉血 5 mL, 4000 r/min 离心 10 min, 取上层血清。利用日立 7600 全自动生化分析仪及试剂盒,测定两组患者肾功能指标:BUN 及 Cr 水平;通过 CKD-EPI 公式计算患者治疗前后 GFR 水平^[17]。

1.5 血清 VEGF、MMP-9 水平检测

分别于治疗前后取两组患者静脉血 5 mL, 4000 r/min 离心 10 min, 取上层血清。采用酶联免疫吸附(ELISA)法,利用全自动酶标仪(贝登医疗有效公司)检测测定两组患者血清中 VEGF、MMP-9 水平。

1.6 统计学处理

采用 SPSS17.0 统计学软件进行分析处理。计数资料以率(%)表示,组间比较采用 χ^2 检验,计量资料以均数±标准差($\bar{x}±s$)表示,组间比较采用 t 检验,以 $P<0.05$ 表示差异有统计学意义。

2 结果

2.1 两组临床疗效的比较

治疗后,对照组患者临床总有效率为 73.33%(22 例);观察组患者临床总有效率为 86.67%(26 例),明显高于对照组($P<0.05$)。见表 1。

表 1 两组患者临床疗效的比较(例)

Table 1 Comparison of the clinical efficacy between two groups(n)

Groups	n	Markedly effective	Effective	Invalid	Total effective rate (%)
Control group	30	16	6	8	73.33
Observation group	30	22	4	4	86.67*

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

2.2 两组不良反应发生情况的比较

治疗后,对照组患者总不良反应率为 10.00%;观察组患者总不良反应率为 3.33%,较对照组明显降低($P<0.05$)。见表 2。

2.3 两组治疗前后肾功能的比较

治疗前,两组血清 BUN、Cr 及 GFR 水平比较差异均无统计学意义($P>0.05$)。治疗后,两组患者血清 BUN、Cr 水平明显低于本组治疗前, GFR 水平明显高于本组治疗前;观察组患者血

清中 BUN、Cr 水平明显低于对照组, GFR 水平明显高于对照组($P<0.05$)。见表 3。

2.4 两组治疗前后血清 VEGF、MMP-9 水平的比较

治疗前,两组血清 VEGF 及 MMP-9 水平比较差异均无统计学意义($P>0.05$)。治疗后,两组血清 VEGF 及 MMP-9 水平均较治疗前明显降低,且观察组血清 VEGF 及 MMP-9 水平均明显低于对照组($P<0.05$)。见表 4。

表 2 两组患者不良反应发生情况的比较(例)

Table 2 Comparison of the occurrence of adverse reactions between two groups (n)

Group	n	Elevated transaminase	Diarrhea	Feeble	Total effective rate (%)
Control group	30	1	1	1	10.00
Observation group	30	0	0	1	3.33*

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

表 3 两组患者治疗前后肾功能水平的比较($\bar{x}\pm s$)Table 3 Comparison of the renal function between two groups before and after treatment($\bar{x}\pm s$)

Groups	n	Time	BUN(mmol/L)	Cr(mmol/L)	GFR(mL/min)
Control group	30	Before treatment	10.58 $\pm$ 0.94	89.73 $\pm$ 9.06	66.57 $\pm$ 6.83
		After treatment	6.88 $\pm$ 0.67 ^a	79.02 $\pm$ 8.22 ^a	73.18 $\pm$ 7.50 ^a
Control group	30	Before treatment	10.36 $\pm$ 0.97	89.90 $\pm$ 9.13	66.14 $\pm$ 6.72
		After treatment	4.50 $\pm$ 0.49 ^a *	70.03 $\pm$ 6.89 ^a *	79.87 $\pm$ 8.16 ^a *

Note: compared with before treatment, ^a $P<0.05$; compared with control group, * $P<0.05$.

表 4 两组患者血清 VEGF、MMP-9 水平的比较 ($\bar{x}\pm s$)Table 4 Comparison of the serum VEGF and MMP-9 levels between two groups of patients before and after treatment ($\bar{x}\pm s$)

Groups	n	Time	VEGF(pg/mL)	MMP-9(ng/L)
Control group	30	Before treatment	419.08 $\pm$ 37.03	146.18 $\pm$ 14.06
		After treatment	389.16 $\pm$ 33.21 ^a	76.18 $\pm$ 7.68 ^a
Observation group	30	Before treatment	420.91 $\pm$ 36.69	145.96 $\pm$ 13.88
		After treatment	360.62 $\pm$ 30.57 ^a *	62.57 $\pm$ 6.75 ^a *

Note: compared with before treatment, ^a $P<0.05$; compared with control group, * $P<0.05$.

3 讨论

IgA 肾病是由环境、遗传因素及免疫因素等多种原因导致的自身免疫性疾病,是一种特殊的肾脏疾病,可通过不同途径损害患者肾脏,其临床表现主要为反复发作的肉眼血尿以及持续性镜下血尿和(或)蛋白尿^[18-20]。近年来,由于人们饮食结构及生活习惯的改变,IgA 肾病的发病率呈逐渐上升趋势。泼尼松为中效糖皮质激素类药物,可以减少蛋白尿、降低终末期肾功能衰竭的风险。临床可用于各种肾病综合征等的治疗^[21,22]。来氟米特为特效免疫抑制剂,能针对免疫反应多个阶段发挥抑制作用。来氟米特能够抑制络氨酸激酶、NF- κ B 活性;抑制二轻乳酸脱氢酶和细胞周期依赖性激酶的活性;此外,还能够抑制细胞黏附分子表达。研究表明来氟米特治疗 IgA 肾病疗效显著,且在改善患者肾脏损伤的同时不会增加不良反应发生的风险^[23]。因此,本研究观察了泼尼松联合来氟米特对 IgA 肾病患者的临床疗效及不良反应情况。本研究结果显示:观察组患者治疗后临床总有效率为 86.67%,明显高于对照组,而总不良反应率为 3.33%,显著低于对照组,表明泼尼松联合来氟米特能有效提高 IgA 肾病患者临床疗效并降低不良反应发生率,具有较好的临床疗效。

肾功能是指肾脏排泄体内代谢废物,维持机体钠、钾、钙等电解质的稳定及酸碱平衡的功能。临床肾功能检查主要包括血肌酐、血尿素氮、尿免疫球蛋白 G、尿白蛋白、尿分泌型免疫球蛋白 A 等。BUN 是指血浆中除蛋白质以外的一种含氮化合物,

它从肾小球滤过而排出体外,在肾功能不全失代偿时,BUN 将升高,所以临床上可以将其作为判断肾小球滤过功能的指标。研究显示 IgA 肾病患者尿素氮水平明显高于正常水平^[24]。Cr 是人体肌肉代谢的产物,与体内肌肉总量关系密切。肌酐是小分子物质,可通过肾小球滤过,在肾小管内很少吸收,每日体内产生的肌酐,几乎全部随尿排出,一般不受尿量影响,临床上检测血肌酐是常用的了解肾功能的主要方法之一。肾病血肌酐、尿素氮高以微小循环损伤,肾小球硬化和基底膜损伤为主要病理变化^[25]。单位时间内两肾生成滤液的量称为肾小球滤过率(GFR),流经肾的血浆约有 1/5 由肾小球滤入囊腔生成原尿,因此 GFR 是衡量肾功能的重要指标之一。本研究结果显示:治疗后,两组患者血清中 BUN、Cr 水平明显低于本组治疗前,GFR 水平明显高于本组治疗前;且观察组患者血清中 BUN、Cr 水平明显低于对照组,GFR 水平明显高于对照组,表明泼尼松联合来氟米特能有效提高糖尿病肾病患者 GFR 水平,缓解肾小球损伤,恢复肾功能。既往研究显示来氟米特作为免疫抑制剂类药物,可通过抑制免疫细胞过度活化,达到平衡细胞因子水平,限制免疫复合物生成的作用^[26]。来氟米特治疗 IgA 肾病患者,可通过抑制炎症反应,在 IgA 肾病的多阶段有效发挥自身作用,抑制肾小球的免疫反应及肾小管的炎症反应,有效改善肾小球硬化持续加重的现象,最终达到对肾小管-间质纤维化进行有效的预防和避免的目的^[27]。由此可见,泼尼松联合来氟米特降低 IgA 肾病患者尿素氮水平,改善氮平衡的作用与抑制免疫细胞过度活化及抑制炎症反应有关,从而进一步增强肾小

管转运功能,达到改善肾功能的作用。

研究表明血清 VEGF 水平与 IgA 肾病患者尿蛋白水平呈正相关,VEGF 可与内皮细胞特异性受体结合,导致肾小球内皮细胞损伤、肾小球硬化等^[28]。基质金属蛋白酶-9(MMP-9)具有降解细胞外基质胶原和非胶原成分的作用。其在 IgA 肾病的发生发展过程中发挥了重要作用^[29]。为进一步研究来氟米特对 IgA 肾病患者肾小球功能的影响,本研究对两组患者治疗前后血清中 VEGF 及 MMP-9 水平进行了比较。VEGF 具有促进血管通透性增加、血管内皮细胞迁移及血管形成等作用,可引起内皮细胞的增殖,对于肾脏血管的形成具有重要影响,其血清水平与肾小球结节样病变程度有关。MMP-9 水平异常是导致细胞外基质降解异常的重要因素。MMP-9 异常表达在肾小球纤维化的进展中起重要作用。研究表明 MMP-9 的含量与 IgA 模型大鼠病情呈正相关^[30]。本次研究结果显示:治疗后,两组患者血清中 VEGF 及 MMP-9 水平明显降低,且观察组患者血清中 VEGF 及 MMP-9 水平明显低于对照组,表明泼尼松联合来氟米特能有效降低 IgA 肾病患者血清中 VEGF 及 MMP-9 水平,进而显著减轻患者肾脏纤维化程度,提高肾脏抗纤维化能力,对肾脏具有一定的保护作用。已有研究显示泼尼松联合来氟米特可通过调节 T 细胞亚群水平,维持细胞因子平衡,调节免疫系统,起到有效抑制血管内皮因子水平的作用,从而抑制肾脏血管活性物质及炎症因子的过度释放。本研究结果与已有报道相符^[31]。

综上所述,泼尼松联合来氟米特治疗 IgA 肾病的临床疗效明显优于单用泼尼松治疗,可更显著改善患者肾脏功能,可能与其降低患者血清 VEGF 及 MMP-9 水平有关。

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