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非布司他对急性痛风性关节炎患者血清 SUA 水平及氧化应激的影响*

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摘要 目的: 研究非布司他治疗急性痛风性关节炎(AGA)患者的临床疗效及对血清尿酸(SUA)水平及氧化应激的影响。**方法:** 研究对象选取我院 2014 年 6 月到 2016 年 10 月收治的 200 例 AGA 患者,采用随机数字法将其分为对照组和观察组,每组各 100 例。对照组患者口服别嘌醇治疗,观察组患者口服非布司他治疗,均连续治疗 24 周。比较两组患者治疗前后各时间点的血清 SUA、8-羟基脱氧鸟苷(8-OHdG)、3-硝基酪氨酸修饰蛋白(3-NT)、甘油三酯(TG)、总胆固醇(TC)、低密度脂蛋白(LDL)、高密度脂蛋白(HDL)水平的变化。**结果:** 治疗后,观察组各时间点的血清 SUA、8-OHdG 和 3-NT 水平均明显低于对照组($P<0.01$)。治疗后,对照组患者的血清 TG、TC、HDL、LDL 水平较治疗前无明显变化($P>0.05$),观察组患者的血清 TG 水平明显低于治疗前($P<0.01$),血清 HDL 水平明显高于治疗前($P<0.01$),而血清 TC 和 LDL 水平比较无明显差异($P>0.05$)。**结论:** 非布司他治疗 AGA 的疗效明显,能有效降低血清 SUA 水平,抑制氧化应激状态,并能改善血脂代谢。

关键词: 非布司他;急性痛风性关节炎;疗效;血清尿酸;氧化应激

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Effect of Febuxostat on the Level of Serum UA and Oxidative Stress in Patients with Acute Gouty Arthritis*

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ABSTRACT Objective: To study the clinical efficacy of febuxostat in the treatment of acute gouty arthritis (AGA) and the effect of on the serum uric acid (SUA) level and oxidative stress. **Methods:** 200 cases of AGA patients in our hospital from June 2014 to October 2016 were randomly divided into the control group and the observation group, with 100 cases in each group. The control group was treated with allopurinol, while the observation group was treated with febuxostat, both groups were treated for 24 weeks. The serum SUA levels, 8-hydroxydeoxyguanosine (8-OHdG), 3-nitro tyrosine modified protein (3-NT), triglyceride (TG), total cholesterol (TC), low density lipoprotein (LDL), high density lipoprotein (HDL) before and after treatment at different time points were compared between two groups. **Results:** After treatment, the serum SUA, 8-OHdG and 3-NT levels in the observation group at each time points were significantly lower of than those of the control group ($P<0.01$), the serum TG, TC, HDL, LDL levels of control group showed no significant difference than those before treatment ($P>0.05$) the serum TG level of observation group was lower than that before treatment ($P<0.01$), while the serum HDL level was higher than that before treatment ($P<0.01$), serum TC, LDL levels showed no significant difference ($P>0.05$). **Conclusion:** Febuxostat could effectively reduce the level of serum SUA, inhibit the oxidative stress, and improve blood lipid metabolism in the treatment of patients with AGA.

Key words: Febuxostat; Acute gouty arthritis; Curative effect; SUA; Oxidative stress

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前言

急性痛风性关节炎(Acute gouty arthritis, AGA)是临床常见的风湿病,是痛风发病的最早期临床表现,患者主要表现为突发的双下肢关节红肿和功能受限,并伴有刀割、咬噬样疼痛感,病情可累及损伤骨质、肾脏,且多合并有高血脂症、糖尿病、高血压等疾病,严重甚至可导致尿毒症^[1]。研究表明^[2]先天性嘌呤

代谢异常是 AGA 发生的主要原因,血清 SUA 持续性增高,细胞外液尿酸盐(MSU)过饱和,以晶体形式析出并沉积于关节滑膜、软骨等部位,刺激关节部位大量炎症因子释放,出现局限性关节滑膜炎,表现出关节红肿热痛及功能受限,严重影响患者的生活质量。伴随着人们饮食结构的改变及生活质量提高,暴饮暴食现象较为普遍,导致 AGA 发病率呈逐年上升之势^[3],如何治疗 AGA 也成为临床关注重点。

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目前,药物仍是 AGA 的首选治疗方案,常用药物包括别嘌醇、非布司他等,其中别嘌醇常用于高尿酸血症治疗,但其存在药物不耐受现象,影响其治疗疗效^[4]。非布司他是新一代选择性黄嘌呤氧化酶抑制剂^[5],可长期用于伴痛风症状的高尿酸血症治疗,同时是美国治疗该病的唯一批准药物。研究证实氧化应激反应在 AGA 发生发展过程中发挥重要作用,因此,治疗 AGA 时需考虑对氧化应激反应的抑制^[6]。因此,本研究主要探讨了非布司他对急性痛风性关节炎患者血清 SUA 水平及氧化应激的影响,旨在为临床提供指导。

1 资料与方法

1.1 一般资料

研究对象选取我院 2014 年 6 月到 2016 年 10 月间收治的 200 例 AGA 患者,纳入标准^[7]:① 均符合 ARA《痛风性关节炎诊断标准》中关于 AGA 诊断标准,并伴有典型临床症状;② 无合并严重的心脑血管、肝肾肺等器官组织疾病;③ 无合并其他风湿性疾病;④ 均自愿参加并签署知情同意书。排除标准:① 合并血液系统、免疫系统、中枢神经系统等严重疾病者;② 伴有恶性肿瘤者;③ 放化疗、药物等因素所致的 AGA;④ 合并其他部位的严重炎症反应;⑤ 治疗期间服用影响 SUA 代谢药物。采用随机数字法将其分为对照组和观察组,每组各 100 例。对照组患者男性 67 例、女性 33 例,年龄在 34~71 岁,平均年龄为(47.59±8.43)岁,病程在 4 个月~11 年,平均病程为(5.27±2.08)年;观察组患者男性 69 例、女性 31 例,年龄在 33~73 岁,平均年龄为(48.13±8.50)岁,病程在 3 个月~10 年,平均病程为(5.21±2.12)年。两组患者在性别、年龄、病程等一般资料比较,差异均无统计学意义($P>0.05$),具可比性。

1.2 治疗方法

对照组患者口服别嘌醇(重庆青阳药业有限公司治疗,

H50021422,50.0 mg),剂量:300.0 mg/d,频率:3 次/d;观察组患者口服非布司他(万邦生化医药股份有限公司,H20130058,40.0 mg)治疗,剂量:80.0 mg/d,频率:3 次/d。所有患者均连续治疗 24 周,治疗期间密切观察患者的病情变化。

1.3 观察指标

① 比较两组患者治疗前、治疗后 4、8、12、16、20 及 24 周的血清 SUA 水平;② 比较两组患者治疗前后的血清 8-羟基脱氧鸟苷(8-OHdG)和 3-硝基络氨酸修饰蛋白(3-NT)等氧化应激标志物水平;③ 比较两组患者治疗前后的血清甘油三酯(TG)、总胆固醇(TC)、低密度脂蛋白(LDL)、高密度脂蛋白(HDL)水平。

1.4 检测方法

无菌抽取患者外周肘静脉血 3.0 mL,静置 10.0 min,放入 3000 r/min 离心机中离心 10.0 min,分离出血清,放置于-20℃冰箱中保持待测,采用 SUNOAB-1018 全自动生化分析仪(上海泰益医疗仪器设备有限公司)检测血清 SUA 水平,采用酶联免疫吸附法(ELISA)检测血清 8-OHdG 和 3-NT 水平,试剂盒由上海恒远生物科技有限公司提供,所有步骤均严格参照操作说明书进行。

1.5 统计学方法

本研究所有数据均由 SPSS 21.0 处理分析,计量资料采用均数±标准差形式表示,并进行 t 检验;而计数资料以率(n%)表示,采用 χ^2 检验,以 $P<0.05$ 表示差异具有统计学意义。

2 结果

2.1 两组患者治疗前后各时间的血清 SUA 水平比较

两组患者治疗前的血清 SUA 水平比较差异无统计学意义($P>0.05$);治疗后不同时间,两组患者的血清 SUA 水平均较治疗前明显降低,且观察组患者治疗后各时间点的血清 SUA 水平均明显低于对照组($P<0.01$),详情见表 1。

表 1 两组患者治疗前后各时间的血清 SUA 水平比较($\bar{x}\pm s$)

Table 1 Comparison of the serum SUA levels between the two groups before and after treatment($\bar{x}\pm s$)

Group	Serum SUA level($\mu\text{mol/L}$)						
	Before treatment	At 4 weeks after treatment	At 8 weeks after treatment	At 12 weeks after treatment	At 16 weeks after treatment	At 20 weeks after treatment	At 24 weeks after treatment
Control group (n=100)	547.83±66.92	424.35±70.81 ^①	419.56±64.29 ^①	415.92±66.13 ^①	420.51±62.08 ^①	423.75±58.63 ^①	402.15±54.43 ^①
Observation group (n=100)	551.37±67.06	378.14±59.28 ^①	380.49±60.44 ^①	374.23±57.64 ^①	372.90±56.15 ^①	376.44±55.80 ^①	377.52±54.26 ^①
P		0.00	0.00	0.00	0.00	0.00	0.00

Note: ① compared with before treatment, $P<0.05$.

2.2 两组患者治疗前后的血清 8-OHdG 和 3-NT 水平比较

两组患者治疗前的血清 8-OHdG 和 3-NT 水平比较差异均无统计学意义($P>0.05$);治疗后 24 周,观察组患者的血清 8-OHdG 和 3-NT 水平均明显低于对照组($P<0.01$),详情见表 2。

2.3 两组患者治疗前后的血脂指标比较

两组患者治疗前的血清 TG、TC、HDL、LDL 水平比较差异均无统计学意义($P>0.05$);治疗后 24 周,对照组患者的血清 TG、TC、HDL、LDL 水平较治疗前无明显变化($P>0.05$),观察组

患者的血清 TG 水平明显低于治疗前($P<0.01$),血清 HDL 水平明显高于治疗前($P<0.01$),而血清 TC 和 LDL 水平比较无明显差异($P>0.05$),详情见表 3。

3 讨论

急性痛风性关节炎是自身嘌呤代谢紊乱引起的代谢性疾病,其病情具有难治愈、易复发的特点^[8],可导致关节出现红肿热痛表现,甚至可导致关节畸形,如不及时治疗,可引起痛风性

表 2 两组患者治疗前后的血清 8-OHdG 和 3-NT 水平比较($\bar{x} \pm s$)Table 2 Comparison of the serum 8-OHdG and 3-NT levels before and after treatment between two groups($\bar{x} \pm s$)

Group	8-OHdG(ng/ml)		3-NT(nM)	
	Before treatment	After treatment	Before treatment	After treatment
Control group (n=100)	2.01± 0.87	1.13± 0.56 ^①	33.17± 8.85	28.44± 6.71 ^①
Observation group (n=100)	1.98± 0.84	0.84± 0.41 ^①	33.26± 8.90	24.15± 5.28 ^①
P	0.80	0.00	0.94	0.00

Note: ① compared with before treatment, P<0.05.

表 3 两组患者治疗前后的血脂指标比较($\bar{x} \pm s$, mmol/L)Table 3 Comparison of the blood lipid indexes before and after treatment between two groups($\bar{x} \pm s$, mmol/L)

Time	Group	TC	TG	HDL	LDL
Before treatment	Control group (n=100)	5.01± 0.62	3.54± 0.58	1.13± 0.27	3.07± 0.52
	Observation group (n=100)	4.97± 0.61	3.57± 0.55	1.16± 0.30	3.04± 0.49
P	>0.05	>0.05	>0.05	>0.05	>0.05
After treatment	Control group (n=100)	4.57± 0.56	2.80± 0.43	1.22± 0.31	2.87± 0.45
	Observation group (n=100)	4.39± 0.53	2.37± 0.38 ^①	1.34± 0.33 ^①	2.73± 0.47
P		0.18	0.00	0.00	0.20

Note: ① compared with before treatment, P<0.05.

肾病、高血压发生。研究表明^[9]血清 SUA 水平过高是急性痛风性关节炎发病的重要原因,细胞外液 MSU 达到过饱和,以晶体形式析出,并循环沉积于软组织、关节软骨、滑膜及肾脏等部位。同时,MSU 结晶又可刺激机体吞噬细胞、炎症因子、TOLL 样受体活性,通过介导急性痛风性关节炎炎症反应,导致骨质及肾脏的受损^[10]。因此,降低血清 SUA 水平、减少 MSU 结晶在关节及肾脏部位的析出沉积对减轻关节组织破坏及控制急性痛风性关节炎患者病情有着重要作用。目前,药物仍是急性痛风性关节炎的首选治疗方法,临床用于治疗的药物种类较多,包括非甾体类抗炎药、秋水仙碱、肾上腺糖皮质激素或 ACTH 等,但以上药物存在有明显的胃肠道反应、骨髓抑制及肝肾损伤等不良反应,且患者耐受度较低,极大限制其临床应用^[11]。

别嘌醇是目前唯一能抑制 SUA 合成的药物,其自身和代谢产物均能抑制黄嘌呤氧化酶活性^[12],阻断次黄嘌呤及黄嘌呤合成 SUA 途径,从而抑制 SUA 合成,降低血液中 SUA 浓度,减少 MSU 结晶在关节组织及肾脏沉积,从而改善患者病情。但研究显示^[13,14]别嘌醇虽能有效改善患者病情,但存在着明显的不良反应,轻者出现恶心、呕吐、皮疹、胃肠不适等^[15],长期使用则可能导致骨髓抑制、脱发、贫血、肝功能损害等严重不良反应^[16],影响其治疗疗效。因此,选择更为高效、安全的治疗急性痛风性关节炎药物,已成为临床重点研究课题。非布司他是新一代选择性黄嘌呤氧化酶抑制剂,其药效较别嘌醇具有对黄嘌呤氧化酶更高选择性,同时对嘌呤、嘧啶合成及代谢酶无明显影响,从而避免别嘌醇对其他酶类抑制产生的不良反应^[17]。药理学研究显示^[18,19]非布司他与黄嘌呤氧化酶形成的复合物稳定性极高,能持续、高效的抑制 SUA 合成,其疗效较别嘌醇明显更强,是目前美国唯一批准长期治疗痛风伴高尿酸

血症药物^[20]。本研究结果显示观察组治疗后各时间点的血清 SUA 水平均明显低于对照组,同时 TG 水平明显降低,而 HDL 水平升高,表明非布司他具有降低血清 SUA 同时,还有一定调脂作用^[21,22]。氧化应激反应在急性痛风性关节炎起病和发展中起着重要作用,且有研究小时^[23]血清 SUA 水平增加可加重机体氧化应激反应,两者呈相关刺激关系,共同恶化病情,机体氧化应激反应也可作为患者病情评估指标^[24]。血清 8-OHdG 和 3-NT 是机体氧化应激反应的敏感性标志物,能准确反映机体氧化应激反应程度^[25]。本研究结果显示观察组治疗后的血清 8-OHdG 和 3-NT 水平均明显低于对照组,证实非布司他对氧化应激反应改善效果更佳。

综上所述,非布司他治疗 AGA 的临床疗效明显,能有效降低血清 SUA 水平,抑制氧化应激状态,并能改善血脂代谢。

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