

doi: 10.13241/j.cnki.pmb.2020.10.030

小剂量降尿酸药物治疗肾移植后高尿酸血症的疗效及安全性分析*

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摘要 目的:探讨小剂量降尿酸药物治疗肾移植后高尿酸血症的疗效及安全性。**方法:**选择2017年5月至2019年5月于门诊随诊的肾移植后高尿酸血症患者80例进行研究,以随机数表法分为A组(n=28)、B组(n=26)和C组(n=26)。A组给予非布司他(20 mg qd)治疗,B组给予苯溴马隆(25 mg qd)治疗,C组给予别嘌醇(100 mg qd)治疗。比较两组患者的临床疗效、血尿酸(sUA)、尿素氮(BUN)、血肌酐(sCr)、估算肾小球滤过率(eGFR)水平变化情况及不良反应发生情况。**结果:**治疗4周后,三组总有效率分别为89.29%、88.46%、84.62%,比较差异无显著性意义($P>0.05$);治疗前,三组血尿酸水平无显著差异;治疗后,三组血尿酸水平有所改善,但治疗后三组间血尿酸水平差异无显著性意义;治疗前,三组肾功能水平无显著差异;治疗后肾功能变化无显著性意义;治疗后,A组不良反应总发生率为7.14%,显著低于B组的30.77%,C组的34.62%,差异有显著性意义($P<0.05$)。**结论:**在肾移植后高尿酸血症患者中应用小剂量非布司他、苯溴马隆、别嘌醇三种不同的降尿酸药物均能有效降低血尿酸,但未观察到改善肾功能,非布司他显示出更少的副作用。

关键词:小剂量;降尿酸药;肾移植;高尿酸血症;安全性

中图分类号:R692;R617 **文献标识码:**A **文章编号:**1673-6273(2020)10-1933-05

Efficacy and Safety of Low Dose Uric Acid Lowering Drugs in the Treatment of Hyperuricemia after Renal Transplantation*

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ABSTRACT Objective: To study efficacy and safety of low dose uric acid lowering drugs in the treatment of hyperuricemia after renal transplantation. **Methods:** 80 patients with hyperuricemia after kidney transplantation who were followed up in outpatient clinics from May 2017 to May 2019 were enrolled for the study, and were divided into group A (n=28), group B (n=26) and group C (n=26) by random number table. Group A was treated with febuxostat (20 mg qd), group B with benzbromalone (25 mg qd), and group C with allopurinol (100 mg qd). The clinical efficacy, serum uric acid (sUA), urea nitrogen (BUN), serum creatinine (sCr), estimated glomerular filtration rate (eGFR) and the occurrence of adverse reactions of the two groups were compared. **Results:** After 4 weeks of treatment, the total effective rates of the three groups were 89.29%, 88.46% and 84.62%, respectively, with no significant difference ($P>0.05$). Before treatment, there was no significant difference in serum uric acid levels among the three groups. After treatment, uric acid levels in the blood of the three groups were improved, but no significant difference in serum uric acid levels among the three groups after treatment. Before treatment, there was no significant difference in renal function among the three groups. There was no significant change in renal function after treatment. After treatment, the overall incidence of adverse reactions in group A was 7.14%, significantly lower than that in group B (30.77%) and group C (34.62%), with significant difference ($P<0.05$). **Conclusion:** Febulostat, benzbromalone and allopurinol were all effective in lowering uric acid in patients with hyperuricemia after kidney transplantation, but no improvement in renal function was observed, febuxostat shows fewer side effects.

Key words: Low dose; Uric acid lowering drugs; Renal transplantation; Hyperuricemia; Safety

Chinese Library Classification(CLC): R692; R617 **Document code:** A

Article ID: 1673-6273(2020)10-1933-05

* 基金项目:国家自然科学基金项目(81700675);2019年度惠州市医疗卫生类科技计划项目(2019Y049)

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(收稿日期:2019-12-28 接受日期:2020-01-18)

前言

肾移植治疗的开展已经显著改善了尿毒症患者的生存质量,而合并高尿酸血症在肾移植术后患者中是很常见的现象,研究显示,肾移植术后发生高尿酸血症的几率为 40%-50%,甚至可高达 82%^[1]。高尿酸血症可以导致肾脏小动脉发生透明变性、肾小管损伤乃至肾间质纤维化,血清尿酸水平的升高会影响移植肾和肾移植受者的长期存活情况^[2,3]。如何优化肾移植术后高尿酸血症的干预方案是目前临床上亟待解决的问题。目前应用较广的降尿酸药物包括苯溴马隆、别嘌醇、非布司他,其中别嘌醇是最常用的药物,能抑制尿酸的生成,但该药物不良反应较多^[4,5]。苯溴马隆是促进尿酸排泄药物,能有效降低肾功能正常或轻度肾损害患者血尿酸水平,但对于重度肾功能损害患者临床上禁用苯溴马隆^[6]。非布司他为新型药物,是一种选择性抑制黄嘌呤氧化酶,具有不良反应发生率低的特点^[7]。但临床关于这三种药物在肾移植患者中使用的效果及副作用差异,目前尚缺乏前瞻性随机对照研究数据,同时,肾移植患者都是单侧供肾,部分供肾本身功能有一定程度的异常,并且长期暴露在各种可能存在肾毒性的药物之下,肾移植患者高尿酸血症的治疗存在更多的未知因素,该类患者的降尿酸治疗在药物种类选择及剂量选择方面均值得探索。本研究旨在探讨小剂量应用不同降尿酸药物治疗肾移植后高尿酸血症患者的疗效及安全性,现报道如下。

1 资料与方法

1.1 一般资料

选择 2017 年 5 月至 2019 年 5 月于惠州市中心人民医院及广东省中医院随诊的肾移植术后合并高尿酸血症的 80 例患者进行研究。以随机数表法分为 A 组、B 组和 C 组, A 组 28 例,其中男 15 例,女 13 例;年龄 42-70 岁,平均(56.84±5.23)岁;原发病为慢性肾小球肾炎,供肾均来自尸体肾。B 组男 14 例,女 12 例;年龄 45-69 岁,平均(58.93±5.35)岁;原发病为慢性肾小球肾炎,供肾均来自尸体肾。C 组男 15 例,女 11 例,年龄 44-69 岁,平均(58.91±5.29)岁;原发病为慢性肾小球肾炎,供肾均来自尸体肾,三组患者抗排斥方案均为"他克莫司、吗替麦考酚酯、强的松。三组基线资料无统计学差异,具有可

比性。

纳入标准:(1)接受生活指导 3 个月以上仍存在血清尿酸 $\geq 420 \mu\text{mol/L}$;(2)年龄 18-70 岁;(3)临床相关病史及治疗记录完整;(4)签署知情同意书并能遵守研究方案要求。排除标准:(1)肝功能异常者;(2)血液系统异常者;(3)未控制的高血压;(4)未控制的糖尿病患者;(5)消化道溃疡活动期患者;(6)服用噻嗪类利尿剂者;(7)合并泌尿系结石的患者;(8)估算肾小球滤过率(eGFR) $<30 \text{ mL/min/1.73 m}^2$ 的患者;(9)白细胞抗原 HLA-B* 5801 检测阳性的患者;(10)服用氯沙坦的患者。

1.2 方法

所有患者均给予生活指导,保持低糖、低盐及低脂饮食;A 组给予非布司他:非布司他(规格 40 mg,厂家:江苏恒瑞医药股份有限公司,国药准字 H20130081)20 mg,每日 1 次,口服;B 组给予苯溴马隆:苯溴马隆(规格 50 mg,厂家:宜昌长江药业有限公司,国药准字 H20040348)25 mg,每日 1 次,口服;C 组采用别嘌醇:别嘌醇(规格 100 mg,厂家:上海信谊万象药业股份有限公司,国药准字 H31020334)100 mg,每日 1 次,口服。所有患者均上午空腹用药,三组均连续治疗时间超过 4 周。

1.3 观察指标

治疗前及治疗 4 周后抽取肘静脉血 4 mL,3500 r·min⁻¹ 离心 10 min,提取血清,采用酶联免疫吸附试验(ELISA)测定血尿素氮(BUN)、血肌酐(sCr)水平;采用全自动生化分析仪测血尿酸(sUA);估算肾小球滤过率(eGFR)应用 CKD-EPI 公式进行计算;记录不良反应发生情况。

疗效评定标准^[8]:显效:血尿酸降低 $>30\%$;有效:血尿酸降低 $>15\%$;无效:无明显改善或加重。

1.4 统计学分析

以 SPSS22.0 软件包处理,计量资料均用均数 $\pm$ 标准差($\bar{x} \pm s$)表示,组间比较使用独立样本 t 检验,多组比较采用方差分析,计数资料以率表示, χ^2 检验, $P < 0.05$ 表示差异具有统计学意义。

2 结果

2.1 三组疗效比较

治疗后,三组总有效率分别为 89.29%、88.46%、84.62%,比较差异无显著性意义($P > 0.05$),见表 1。

表 1 三组疗效比较[n(%)]

Table 1 Comparison of efficacy among the three groups[n(%)]

Groups	n	Excellent	Effective	Invalid	Total effective rate
Group A	28	14(50.00)	11(39.29)	3(10.71)	25(89.29)
Group B	26	10(38.46)	13(50.00)	3(11.54)	23(88.46)
Group C	26	13(50.00)	9(34.62)	4(15.38)	22(84.62)
χ^2 value					0.301
P value					0.860

2.2 三组血尿酸水平比较

治疗前,三组血尿酸水平无显著差异;治疗后,三组血尿酸水平均较前有所改善,但治疗后三组间血尿酸水平差异无显著

性意义;见表 2。

2.3 三组肾功能水平比较

治疗前,三组肾功能基线水平无显著差异;治疗后三组肾

功能较前变化无统计学意义,见表3。

表2 三组血尿酸水平比较($\bar{x} \pm s$, $\mu\text{mol/L}$)Table 2 Comparison of serum uric acid levels among the three groups($\bar{x} \pm s$, $\mu\text{mol/L}$)

Groups	n	Serum uric acid	
		Before the treatment	After treatment
Group A	28	512.34 $\pm$ 43.81	320.35 $\pm$ 23.14
Group B	26	517.56 $\pm$ 44.25	322.65 $\pm$ 37.81
Group C	26	520.31 $\pm$ 43.96	332.56 $\pm$ 42.35
F value		0.229	0.905
P value		0.795	0.409

表3 三组肾功能水平比较($\bar{x} \pm s$)Table 3 Comparison of renal function levels among the three groups($\bar{x} \pm s$)

Groups	n	BUN(mmol/L)		eGFR(mL/min/1.73 m ²)		sCr($\mu\text{mol/L}$)	
		Before the treatment	After treatment	Before the treatment	After treatment	Before the treatment	After treatment
Group A	28	5.39 $\pm$ 1.21	4.89 $\pm$ 1.07	64.95 $\pm$ 12.21	65.06 $\pm$ 10.01	84.67 $\pm$ 11.27	81.52 $\pm$ 9.02
Group B	26	5.42 $\pm$ 1.25	4.85 $\pm$ 1.21	65.05 $\pm$ 12.25	64.05 $\pm$ 10.21	84.72 $\pm$ 11.31	83.95 $\pm$ 9.06
Group C	26	5.37 $\pm$ 1.21	4.96 $\pm$ 1.23	64.91 $\pm$ 12.19	63.08 $\pm$ 10.27	84.76 $\pm$ 11.29	84.59 $\pm$ 9.19
F value		0.011	0.059	0.001	0.256	0.000	0.865
P value		0.989	0.943	0.999	0.775	0.999	0.425

2.4 三组不良反应发生情况比较

的30.77%,C组的34.62%,差异有显著性意义($P<0.05$),见表4。

治疗后,A组不良反应总发生率为7.14%,显著低于B组

表4 三组不良反应发生情况比较[n(%)]

Table 4 Comparison of adverse reactions among the three groups[n(%)]

Groups	n	Decreased libido	The rash	Upper abdominal discomfort	Nausea	Total incidence rate
Group A	28	1(3.57)	0(0.00)	0(0.00)	1(3.57)	2(7.14)
Group B	26	2(7.69)	2(7.69)	3(11.54)	1(3.85)	8(30.77)
Group C	26	3(11.54)	2(7.69)	1(3.85)	3(11.54)	9(34.62)
χ^2 value		1.236	2.267	3.887	1.840	6.667
P value		0.539	0.322	0.143	0.398	0.036

3 讨论

高尿酸血症在肾移植术后较为常见,高尿酸血症可以导致肾脏损伤,甚至会导致尿酸性结石,造成严重的泌尿系梗阻,导致肾后性移植肾失功,也会增加心血管疾病的发病风险,影响移植肾及肾移植受者的存活情况^[9,10]。目前研究显示导致肾移植后高尿酸血症主要的原因包括:免疫抑制剂的应用、利尿剂的应用及移植肾对尿酸的排泄减少等^[11,12]。现有研究提示,高尿酸血症主要是通过导致内皮细胞功能异常和炎症反应、引起肾脏血流动力学改变、及肾小球肥厚机制等对肾脏产生致病作用^[13-15]。所以肾移植后高尿酸血症是属于需要积极干预的情况。

目前国内有少量研究探讨肾移植术后高尿酸血症患者降尿酸药物的应用选择^[16,17]。别嘌醇是一种嘌呤氧化酶抑制剂,通过抑制还原型黄嘌呤氧化酶的活性,减少尿酸生成,在肾功

能下降的情况下要相应地做出剂量调整,肾小球滤过率低于60 mL/min时要减量,肾小球滤过率低于15 mL/min的情况则要禁用。别嘌醇可导致严重的"别嘌呤醇超敏反应综合征",发生剥脱性皮炎,死亡率达20%~25%,这种严重过敏反应与剂量及白细胞抗原HLA-B*5801相关,使用别嘌醇之前应常规进行该项检查,阳性者应避免使用^[18-20]。苯溴马隆是一种增加尿酸排泄的代表性药物,通过抑制尿酸盐在肾小管的再吸收,增加排泄尿酸盐,可以降低血尿酸的浓度,但在肾功能不全的患者中使用也受到限制,肾小球滤过率低于20 mL/min者禁用^[21-23]。非布司他则是一种新型非嘌呤类选择性黄嘌呤氧化酶抑制剂,较别嘌醇优胜之处在于对氧化型和还原型的黄嘌呤氧化酶均有显著的抑制作用,因具有独特的非嘌呤分子结构,使其对黄嘌呤氧化酶的抑制具有高度选择性,不影响嘧啶和嘌呤代谢路径中的其他相关酶,不影响嘧啶及嘌呤的正常代谢^[24-26]。不同的药

物使用方案治疗下肾移植术后高尿酸血症患者的血尿酸控制效果、肾功能变化情况、不良反应等不同^[27,28]。本研究采用小剂量降尿酸药物治疗肾移植术后高尿酸血症,结果显示非布司他(20 mg qd)、苯溴马隆(25 mg qd)、别嘌醇(100 mg qd)均能实现降低肾移植术后高尿酸血症患者血尿酸的目的,三组患者总有效率分别为 89.29%、88.46%、84.62%,效果相当,未显示出效果的差异,提示在无相关禁忌证的情况下,三种药物均可适用于肾移植后高尿酸血症患者。而本研究结果显示,使用非布司他治疗的患者不良反应发生率为 7.14%,低于其他两组患者,提示高危患者可优先选择非布司他,以减少治疗过程中的不良事件发生率。

至于干预器官移植术后高尿酸血症是否能改善肾功能,目前有少量研究结果已经发表。Tojimbara T^[29]等回顾性分析了 22 名肾移植后高尿酸血症患者的诊疗过程,包括了起始即使用非布司他治疗的患者、起始使用苯溴马隆继而改用非布司他治疗的患者及起始使用别嘌醇继而改用非布司他治疗的患者,随诊结束时将血尿酸从 $480 \pm 48 \mu\text{mol/L}$ 降至 $342 \pm 42 \mu\text{mol/L}$,而患者估算肾小球滤过率(eGFR)无改善。Baek CH^[30]等回顾性分析了 31 名肾移植后高尿酸血症患者的诊疗资料,这些患者接受了非布司他、苯溴马隆或别嘌醇治疗,在治疗 12 个月时,非布司他的平均血清尿酸水平为 $280.77 \pm 78.52 \mu\text{mol/L}$,苯溴马隆的平均尿酸水平为 $332.52 \pm 72.57 \mu\text{mol/L}$,别嘌醇组的平均尿酸水平为 $363.45 \pm 60.08 \mu\text{mol/L}$,均达到降尿酸治疗的目标值,但是,对患者估算肾小球滤过率(eGFR)并没有明显影响。本研究前瞻性小剂量使用非布司他、苯溴马隆或别嘌醇三种降尿酸药物干预肾移植术后高尿酸血症患者,治疗 4 周时虽然明显降低患者血尿酸水平,亦未能观察到肾功能的改善,结论和以上研究吻合,原因可能是肾移植术后患者的肾功能受到诸多因素的影响,如移植肾供体本身的肾功能状态、抗排斥药物剂量不足的情况下可导致排斥反应、抗排斥药物剂量过高的情况下可导致肾毒性、移植肾血管吻合情况等,高尿酸血症对肾功能的影响只是其中一个因素。居于本研究及以上提及的两个研究均属小样本研究,观察时间也较短,降尿酸治疗是否能改善肾移植术后高尿酸血症患者肾功能、延长移植物存活时间及降低肾移植受体死亡率仍需进一步探讨。

综上所述,在肾移植后高尿酸血症患者中应用小剂量非布司他、苯溴马隆、别嘌醇三种不同的降尿酸药物均能有效降低血尿酸,但未观察到能改善患者肾功能,其中非布司他副作用较少。降尿酸治疗对肾移植术后高尿酸血症患者能产生怎样的获益,有待进行多中心大样本研究进一步明确。

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