

doi: 10.13241/j.cnki.pmb.2020.05.027

肾移植术后排斥反应患者肠道菌群、血小板参数的变化 及其危险因素分析*

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摘要 目的:探讨肾移植术后排斥反应(AR)患者肠道菌群、血小板参数的变化及术后AR的危险因素。**方法:**选择接受肾移植的患者150例,术后发生AR 26例作为研究组,未发生AR 124例作为对照组,比较两组术前、术后肠道菌群变化及血小板参数变化,分析肾移植术后AR的危险因素。**结果:**术后研究组肠道乳酸杆菌、双歧杆菌的数量、双歧杆菌/肠杆菌较对照组减少,肠杆菌、肠球菌的数量较对照组增多($P<0.05$)。研究组术后5 d、7 d血小板比容(PCT)低于对照组,平均血小板容积(MPV)、血小板分布宽度(PDW)、血小板比率(P-LCR)高于对照组($P<0.05$)。多因素Logistic回归分析显示:术后乳酸杆菌数量减少、双歧杆菌数量减少、双歧杆菌/肠杆菌减少,肠杆菌数量增多、肠球菌数量增多,PCT降低、PDW升高、P-LCR升高为肾移植术后AR的危险因素($P<0.05$)。**结论:**肾移植术后AR患者肠道菌群失调,术后PCT降低,MPV、P-LCR升高。患者术后肠道菌群失调、PCT降低、PDW升高、P-LCR升高为AR的危险因素。

关键词:肾移植;排斥反应;肠道菌群;血小板;危险因素

中图分类号:R692;R617 **文献标识码:**A **文章编号:**1673-6273(2020)05-923-04

Changes of Intestinal Flora and Platelet Parameters and Risk Factors in Patients with Acute Rejection after Renal Transplantation*

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ABSTRACT Objective: To analyze the changes of intestinal flora and platelet parameters in patients with acute rejection (AR) after renal transplantation and the risk factors of postoperative AR. **Methods:** 150 cases of renal transplantation were selected, 26 cases of postoperative AR occurred patients were taken as study group, 124 cases of no AR occurred patients were taken as control group. The changes of intestinal flora, platelet parameters before and after operation were compared between the two groups, and analyzed the risk factors of AR after renal transplantation. **Results:** The number of intestinal *Lactobacillus*, *Bifidobacterium* and *Bifidobacterium/Enterobacter* in the study group were less than those in the control group, while the number of *Enterobacter* and *Enterococcus* in the study group were more than those in the control group ($P<0.05$). The platelet specific volume (PCT) of study group at 5 d after operation and 7 d after operation was lower than that of control group, and the mean platelet volume (MPV), platelet distribution width (PDW) and platelet ratio (P-LCR) were higher than those of the control group ($P<0.05$). Multivariate logistic regression analysis showed that the number of *Lactobacillus*, *Bifidobacterium* and *Bifidobacterium/Enterobacter* decreased, the number of *Enterobacter* and *Enterococcus* increased, PCT reduction, PDW elevation and P-LCR elevation were risk factors for AR after renal transplantation ($P<0.05$). **Conclusion:** The intestinal flora of AR patients after renal transplantation is disordered, PCT is decreased, MPV and P-LCR are increased. Postoperative intestinal flora disorder, PCT reduction, PDW elevation and P-LCR elevation are risk factors for AR.

Key words: Renal transplantation; Acute rejection; Intestinal flora; Platelet; Risk factors

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

Article ID: 1673-6273(2020)05-923-04

前言

肾移植是目前临床上治疗终末期肾病患者最有效的方法,

随着手术技术的不断改进和新型免疫抑制剂的应用,肾移植成功率已高达90%以上,但患者术后发生排斥反应(Acute rejection, AR)仍是导致治疗失败的重要原因^[1,2]。对肾移植术后

* 基金项目:国家自然科学基金面上项目(81670596);广西科学技术开发与研究项目(桂科攻 14124003-8)

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(收稿日期:2019-07-21 接受日期:2019-08-17)

AR 及时给予相应治疗对于提高移植存活率具有重要意义。肠道菌群是一个复杂的微生态系统,研究发现,机体肠道菌群与宿主生长发育、物质代谢及免疫功能有密切关系^[3,4]。肾移植术后患者免疫功能的改变可能影响肠道菌群,并引发肠道菌群失调^[5,6]。另有研究发现,在器官移植术后血小板可以促进特异性抗体介导的炎症反应,与 AR 的发生和发展有密切关系^[7]。本研究分析肾移植术后 AR 患者肠道菌群、血小板参数的变化,并分析肾移植术后 AR 的危险因素,旨在为肾移植术后 AR 的防治提供依据,现报道如下。

1 资料与方法

1.1 一般资料

选择 2016 年 1 月至 2019 年 1 月于广西医科大学第二附属医院接受同种异体肾移植的患者 150 例,纳入标准:(1)患者自愿接受同种异体肾移植手术,对研究知情同意,签署知情同意书;(2)患者与供体血性相符,群体反应性抗体级淋巴细胞毒性实验均为阴性,HLA 配型错配 1~4 个位点;(3)患者术前均接受规律血液透析治疗;(4)患者术后均采用泼尼松+霉酚酸酯+他克莫司三联方案抗免疫排斥治疗;(5)患者完成 2 个月的随访观察。排除标准:(1)观察期内应用影响血小板药物者;(2)观察期内服用抗生素者;(3)出现感染者;(4)有心脑血管基础疾病、血液系统疾病者。术后发生 AR 患者 26 例作为研究组,男性 16 例、女性 10 例,年龄 25~62 岁,平均年龄(43.12±4.12)岁;原发疾病:糖尿病肾病 3 例、高血压肾病 6 例、慢性肾小球肾炎 17 例;发生 AR 时间为术后 5~28d,平均(13.78±1.21)d。未发生 AR 患者 124 例作为对照组,其中男性 78 例,女性 46 例,年龄 27~61 岁,平均年龄(44.03±3.78)岁;原发疾病:糖尿病肾病 14 例、高血压肾病 31 例、慢性肾小球肾炎 79 例。两组患者性别构成、年龄和原发疾病比较无统计学差异($P>0.05$),具有可比性。

1.2 AR 的诊断标准^[8]

患者体温升高、尿量较术前一天明显减少,血压升高,移植区域疼痛、肿胀,血肌酐升高 $>104 \mu\text{mol/L}$ 或连续 24h 内血肌酐升高 20%以上,移植区彩超检查显示移植肾肿大、肾动脉阻力指数 >0.75 ,移植肾脏穿刺活检证实免疫排斥反应。

1.3 方法

1.3.1 肠道菌群的检测 分别采集患者术前、术后首次排便的新鲜粪便,置于无菌厌氧采集瓶中,取粪便中心部位样本 0.3 g 放入无菌试管中,加入稀释液至 3 mL,震荡混匀,将标本 10 倍连续稀释至 10^9 倍稀释液,将各浓度稀释液依次接种于培养基上,培养基购置于青岛海博生物有限公司,批号为 HB0323, HB0512, HB0712,于取样后 30 分钟内完成接种。需氧菌培养条件为普通培养箱 37°C 培养 18~24h;厌氧菌培养条件为 Thermo Forma 厌氧手套培养箱培养 48~72h,应用 API 鉴定板鉴定细菌,通过倒置显微镜计算细菌数量,单位为 CFU/g,并换算为 $\log \text{CFU/g}$ 。

1.3.2 血小板参数的检测 分别于术前、术后 3d、术后 5d、术后 7d 采集患者外周静脉血 2 mL,置于乙二胺四乙酸二钾抗凝试管中,应用 Sysmex XE2100 全自动血液分析仪检测血小板参数,包括血小板计数 (Platelet count, PLT)、平均血小板容积 (Mean platelet volume, MPV)、血小板比容 (Plateletcrit, PCT)、血小板分布宽度 (Platelet distribution width, PDW)、血小板比率 (Platelet ratio, P-LCR)。

1.4 统计学方法

应用 SPSS23.0 软件进行统计学分析,计量资料以(均数±标准差)的形式表示,应用 t 检验,应用多因素 Logistic 回归分析肾移植术后 AR 的危险因素, $P<0.05$ 表明差异具有统计学意义。

2 结果

2.1 两组患者术前、术后首次排便肠道菌群比较

两组患者术前肠道乳酸杆菌、肠杆菌、肠球菌、双歧杆菌的数量、双歧杆菌/肠杆菌比较无统计学差异($P>0.05$),术后研究组肠道乳酸杆菌、双歧杆菌的数量、双歧杆菌/肠杆菌显著少于术前,肠杆菌、肠球菌的数量显著多于术前($P<0.05$),对照组乳酸杆菌数量显著少于术前,肠球菌数量显著多于术前($P<0.05$),术后研究组肠道乳酸杆菌、双歧杆菌的数量、双歧杆菌/肠杆菌显著少于对照组,肠杆菌、肠球菌的数量显著多于对照组($P<0.05$),见表 1。

表 1 两组患者术前、术后首次排便肠道菌群比较($\bar{x}\pm s$)

Table 1 Comparison of intestinal flora preoperative and the first defecation after operation between two groups($\bar{x}\pm s$)

Groups	Time	<i>Lactobacillus</i> (log CFU/g)	<i>Enterobacter</i> (log CFU/g)	<i>Enterococcus</i> (log CFU/g)	<i>Bifidobacterium</i> (log CFU/g)	<i>Bifidobacterium/</i> <i>Enterobacter</i>
Study group (n=26)	Preoperative	8.15±1.21	7.78±1.07	7.15±1.12	7.88±1.14	1.01±0.16
	First defecation after operation	5.82±1.11 ^{*#}	9.44±1.18 ^{*#}	9.20±1.54 ^{*#}	6.07±1.28 ^{*#}	0.64±0.12 ^{*#}
Control group (n=124)	Preoperative	8.17±1.25	7.76±1.11	7.13±1.21	7.85±1.22	1.01±0.18
	First defecation after operation	7.02±1.38 [#]	8.35±1.21	8.15±1.43 [#]	7.05±1.73	0.84±0.14

Note: Compared with the control group, ^{*} $P<0.05$; compared with preoperative, [#] $P<0.05$.

2.2 两组患者术前、后血小板参数比较

与术前比较,研究组术后 PLT、PCT 呈降低趋势,MPV、PDW、P-LCR 呈升高趋势,对照组 PLT、PCT 呈降低趋势, P-LCR 呈升高趋势,差异有统计学意义($P<0.05$),对照组术后

MPV、PDW 与术前比较差异无统计学意义($P>0.05$),研究组术后 5d、7d PCT 显著低于对照组,MPV、PDW、P-LCR 显著高于对照组($P<0.05$),见表 2。

表 2 两组患者术前、术后 3d、术后 5d、术后 7d 血小板参数比较($\bar{x} \pm s$)Table 2 Comparison of platelet parameters at preoperative, 3d after operation, 5d after operation and 7d after operation between two groups($\bar{x} \pm s$)

Groups	Time	PLT($10^9/L$)	MPV(fL)	PCT(mL/L)	PDW(fL)	P-LCR(%)
Study group(n=26)	Preoperative	184.52 $\pm$ 8.28	9.98 $\pm$ 0.25	2.21 $\pm$ 0.07	11.37 $\pm$ 0.25	24.42 $\pm$ 0.72
	3d after operation	175.17 $\pm$ 9.12 [#]	10.10 $\pm$ 0.37 [#]	2.02 $\pm$ 0.09 [#]	12.78 $\pm$ 0.33 [#]	26.55 $\pm$ 0.76 [#]
	5d after operation	173.28 $\pm$ 8.86 [#]	11.08 $\pm$ 0.35 ^{*#}	1.37 $\pm$ 0.11 ^{*#}	14.93 $\pm$ 0.42 ^{*#}	31.43 $\pm$ 0.79 ^{*#}
	7d after operation	177.37 $\pm$ 8.73 [#]	11.04 $\pm$ 0.33 ^{*#}	1.42 $\pm$ 0.11 ^{*#}	14.07 $\pm$ 0.37 ^{*#}	30.07 $\pm$ 0.88 ^{*#}
Control group(n=124)	Preoperative	182.87 $\pm$ 10.43	9.96 $\pm$ 0.29	2.23 $\pm$ 0.05	11.79 $\pm$ 0.27	24.44 $\pm$ 0.75
	3d after operation	173.56 $\pm$ 10.78 [#]	10.08 $\pm$ 0.29	2.01 $\pm$ 0.08 [#]	12.53 $\pm$ 0.35	26.17 $\pm$ 0.73 [#]
	5d after operation	171.42 $\pm$ 10.28 [#]	10.12 $\pm$ 0.32	1.58 $\pm$ 0.09 [#]	13.08 $\pm$ 0.35	27.19 $\pm$ 0.82 [#]
	7d after operation	176.11 $\pm$ 10.52 [#]	10.21 $\pm$ 0.38	1.61 $\pm$ 0.11 [#]	13.21 $\pm$ 0.36	27.12 $\pm$ 0.79 [#]

Note: Compared with the control group, * $P < 0.05$; compared with preoperative, [#] $P < 0.05$.

2.3 肾移植术后 AR 的危险因素的多因素 Logistic 回归分析

以是否发生 AR 为因变量,以乳酸杆菌、肠杆菌、肠球菌、双歧杆菌、双歧杆菌/肠杆菌、PCT、PLT、MPV、PDW、P-LCR 为自变量纳入多因素 Logistic 回归分析模型,结果显示:乳酸杆

菌数量减少、肠杆菌数量增多、肠球菌数量增多、双歧杆菌数量减少、双歧杆菌/肠杆菌减少、PCT 降低、PDW 升高、P-LCR 升高为肾移植术后 AR 的危险因素($P < 0.05$),见表 3。

表 3 肾移植术后 AR 的危险因素的多因素 Logistic 回归分析

Table 3 Multivariate Logistic regression analysis of risk factors for AR after renal transplantation

Influencing factors	β value	Standard error	Wald χ^2	P value	OR (95%CI)
<i>Lactobacillus</i> decreased	1.442	0.143	4.744	0.015	1.975(1.263~3.725)
<i>Enterobacter</i> increased	1.236	0.137	5.183	0.000	2.331(1.821~3.897)
<i>Enterococcus</i> increased	1.228	0.128	4.332	0.022	2.152(1.621~3.726)
<i>Bifidobacterium</i> decreased	1.135	0.105	3.971	0.012	2.114(1.572~3.528)
<i>Bifidobacterium/Enterobacter</i> decreased	1.172	0.018	5.253	0.000	2.736(1.918~3.946)
PLT decreased	1.784	0.215	5.642	0.000	2.152(1.424~3.085)
PDW elevation	1.524	0.365	4.835	0.000	1.924(1.324~3.083)
P-LCR elevation	1.442	0.853	5.778	0.000	2.558(1.732~3.283)

3 讨论

AR 是导致肾移植术后肾脏失功的常见原因^[9]。分析肾移植术后 AR 的危险因素,并采取针对性的干预措施对于提高移植肾脏的存活率具有重要的意义。近年来越来越多的研究发现,肠道菌群与机体的免疫状态有密切关系^[10-12]。肠道是一个由肠上皮细胞、大量菌群及黏膜免疫系统组成的复杂的微生态系统,肠道菌群的构成与机体生长发育、代谢及免疫功能密切相关^[13,14]。同种异体器官移植后会产生排斥反应,需要应用免疫抑制剂等药物以降低机体对器官的免疫排斥,然而手术应激、异体器官的移植以及免疫抑制剂的应用均会对宿主机体免疫状态造成影响,进而影响供体肾脏的功能^[15]。叶桂荣等研究报道^[16],肾移植受者、慢性肾脏病患者会发生肠道菌群失调。Dudzicz S 等研究报道显示^[17],肠道植物乳杆菌 299V 可降低肾移植后难治性梭菌感染的发生率。李钢^[18]等报道应用 16S rDNA 高通量测序技术对肾移植术前后肠道菌群进行检测,发现肾移植术后患者免疫状态和肠道菌群变化对 AR 监测具有重要意义。

本研究结果显示,术后研究组肠道乳酸杆菌、双歧杆菌的数量、双歧杆菌/肠杆菌较术前显著降低,肠杆菌、肠球菌的数量较术前显著升高,表明研究组患者术后出现肠道菌群失调。其中肠杆菌和肠球菌属于条件致病菌,正常情况下在机体内少量存在,不会危害人体健康,当肠杆菌和肠球菌大量繁殖时则会对机体产生不利影响^[19]。而双歧杆菌和乳酸杆菌是益生菌,对人体健康有益^[20],同时机体肠道菌群也受机体免疫状态影响^[21]。本研究中研究组患者术后发生肠道菌群失调推测与患者器官移植后免疫功能紊乱及 AR 发生有关。本研究中对照组乳酸杆菌数量较术前显著减少,肠球菌数量较术前显著增多,则可能与手术应激等有关,但术后研究组肠道乳酸杆菌、双歧杆菌的数量、双歧杆菌/肠杆菌显著低于对照组,肠杆菌、肠球菌的数量显著高于对照组,提示发生 AR 的患者肠道紊乱程度更为严重。

本研究还对两组患者术前、术后血小板参数进行了比较。国外已有研究报道,血小板参与器官移植后 AR 的发生^[22,23]。研究发现^[24],血小板异常活化产生多种细胞因子能够促进血小板

与内皮细胞黏附,其中血小板分泌的二磷酸腺苷、血栓素 A2 参与微血栓的形成是 AR 发生的关键环节。也有研究发现^[25,26],器官移植供者和受者血小板抗原 -3 不相容性是导致 AR 发生的重要原因。PCT 是反映单位容积的全血中血小板所占比例^[27],MPV 和 PDW 是从整体上反映血小板体积和分布的指标^[28],而 P-LCR 则是反映大血小板所占比率的指标^[29]。研究组术后 5d、7d PCT 显著低于对照组,表明研究组术后血小板消耗过多。研究组 MPV、P-LCR 显著高于对照组,表明研究组术后血液中大血小板增多,推测主要与患者术后骨髓巨核细胞增生、血小板生成有关,同时也反映了研究组患者血小板活性增高,功能亢进。笔者推测研究组患者术后血小板异常活化,并促进 AR 发生^[30]。本研究还发现乳酸杆菌数量降低、肠杆菌数量升高、肠球菌数量升高、双歧杆菌数量降低、双歧杆菌 / 肠杆菌降低、PCT 降低、PDW 升高、P-LCR 升高为肾移植术后 AR 的危险因素。这也提示了我们在临床工作中可针对以上因素采取干预措施,为肾移植术后 AR 的早期诊断提供依据,从而提高移植肾脏的存活率。

综上所述,肾移植术后 AR 患者肠道菌群失调,表现为条件致病菌增多,益生菌减少。患者术后 5d、7d PCT 显著降低,MPV、P-LCR 显著增高。术后乳酸杆菌数量减少、肠杆菌数量增多、肠球菌数量增多、双歧杆菌数量减少、双歧杆菌 / 肠杆菌减少、PCT 降低、PDW 升高、P-LCR 升高为肾移植术后 AR 的危险因素,值得临床重点关注,以提高移植肾脏的存活率。

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