doi: 10.13241/j.cnki.pmb.2020.20.039

RPLU 术对重度肾积水的上尿路结石患者尿 ET-1、AQP-1、MCP-1 水平的影响 *

李 程 王永胜 王 波 罗家宇 郭新权

（四川大学华西医院眉山医院 眉山市人民医院泌尿外科 四川 眉山 620010）

摘要 目的：探讨后腹腔镜下输尿管切开取石术（RPLU）对重度肾积水的上尿路结石患者尿内皮素 -1（ET-1）、水通道蛋白 -1（AQP-1）、单核细胞趋化蛋白 -1（MCP-1）水平的影响。**方法：**收集 2018 年 4 月 ~2019 年 11 月我院收治的 106 例重度肾积水的上尿路结石患者为研究对象，按照随机数字表法分为对照组和研究组，每组 53 例，对照组采用输尿管镜取石术治疗，研究组采用 RPLU 术治疗，对比两组手术情况，手术前后血红蛋白、肾功能、尿 ET-1、AQP-1、MCP-1 水平，手术并发症发生情况。**结果：**研究组手术时间及住院时间多于对照组，结石清除率高于对照组，比较差异有统计学意义（*P*<0.05）；两组术中出血量、术后排气时间比较差异无统计学意义（*P*>0.05）。术后，两组血红蛋白较术前无显著差异（*P*>0.05）。术后，两组血肌酐及血尿酸氮均下降，两组比较差异无统计学意义（*P*>0.05）。术后，两组尿 ET-1、AQP-1、MCP-1 水平均下降，两组比较无统计学意义（*P*>0.05）。两组并发症总发生率比较无统计学意义（*P*>0.05）。**结论：**RPLU 术是治疗重度肾积水的上尿路结石清除率高，创伤小，可作为重度肾积水伴上尿路结石安全、有效的术式。

关键词：重度肾积水；上尿路结石；后腹腔镜下输尿管切开取石术；内皮素 -1；水通道蛋白 -1；单核细胞趋化蛋白 -1

中图分类号：R693.4；R692.7 **文献标识码：**A **文章编号：**1673-6273（2020）20-3978-05

Effect of RPLU on Urinary ET-1, AQP-1 and MCP-1 Levels in Patients with Upper Urinary Calculi with Severe Hydronephrosis*

LI Cheng, WANG Yong-sheng, WANG Bo, LUO Jia-yu, GUO Xin-quan

(Department of Urology, Meishan hospital, West China Hospital, Sichuan University Meishan people's Hospital, Meishan, Sichuan, 620010, China)

ABSTRACT Objective: To investigate the effect of retroperitoneal laparoscopic ureterolithotomy (RPLU) on urinary endothelin -1 (ET-1), aquaporin -1(AQP-1) and monocyte chemoattractant protein -1(MCP-1) levels in patients with upper urinary calculi with severe hydronephrosis. **Methods:** 106 patients with upper urinary tract calculi with severe hydronephrosis admitted to our hospital from April 2018 to November 2019 were collected as research objects and divided into control group and research group according to random number table method, 53 cases in each group. The control group was treated with ureteroscopic lithotomy, and the research group was treated with RPLU. The operation conditions, including hemoglobin, renal function, urine ET-1, AQP-1, MCP-1 levels before and after the operation, and the occurrence of surgical complications of the two groups were compared. **Results:** The operation time and hospitalization time of the study group were longer than those of the control group, and the stone clearance rate was higher than that of the control group, the difference was statistically significant (*P*<0.05). There was no significant difference in intraoperative blood loss and postoperative exhaust time between the two groups (*P*>0.05). After operation, there was no significant difference in hemoglobin between the two groups (*P*>0.05). After operation, serum creatinine and uric acid and nitrogen in both groups decreased, and there was no significant difference between the two groups (*P*>0.05). After the operation, the urine ET-1, AQP-1 and MCP-1 levels in both groups decreased, the difference was not statistically significant (*P*>0.05). There was no statistical difference in the total incidence of complications between the two groups (*P*>0.05). **Conclusion:** RPLU is a safe and effective method for the treatment of severe hydronephrosis with upper urinary tract stones due to its high clearance rate and small trauma.

Key words: Severe hydronephrosis; Upper urinary calculi; Retroperitoneoscopic ureterolithotomy: Endothelin-1; Aquaporin-1; Monocyte chemotactic protein -1

Chinese Library Classification(CLC): R693.4; R692.7 Document code: A

Article ID: 1673-6273（2020）20-3978-05

* 基金项目：四川省科研基金资助项目（2018HU368）

作者简介：李程（1977-），男，本科，副主任医师，研究方向：泌尿外科，E-mail: hejiahuan1811@21cn.com

（收稿日期：2020-05-05 接受日期：2020-05-29）

前言

上尿路结石以血尿、绞痛为主要症状，未经及时处理能够引起结石梗阻，导致严重肾积水，且可继发肾功能损伤、感染等，甚至危及机体生命安全[1,2]。调查研究报道[3,4]，上尿路结石是引起成人肾积水的最主要因素，早期症状不明显，结石长期梗阻能够导致重度肾积水，明显影响患者肾功能。临床对于肾积水严重且结石较大者可选择手术切开取石，其取石效果肯定，但切口较长，可对机体产生明显的应激反应，不利于术后恢复[5]。近年来医学技术的不断发展，多种微创术式已成为治疗重度肾积水的上尿路结石的主要术式。尽管后腹腔镜下输尿管切开取石术（RPLU）的操作难度较大，但有研究报道[6]，RPLU 术治疗上尿路结石方面能够达到和既往开放取石术相似的取石效果。近年来有研究发现[7,8]，尿液中多种生物标志物在肾积水患者中的表达产生了改变，其能够反映肾积水程度，评价术后恢复情况。本研究主要分析 RPLU 术对重度肾积水的上尿路结石患者相关尿细胞因子的影响，为此类疾病的治疗提供参考依据。

1 资料与方法

1.1 一般资料

106 例重度肾积水上尿路结石患者入选标准：符合上尿路结石诊断标准[9]：1.结石部位明显压痛、腰背部及肾区叩压痛明显，2.尿常规检查能够发现镜下血尿，经 X 线平片、B 超及静脉尿路造影能够提示结石大小、部位及数目等情况；合并单侧重度肾积水；输尿管中上段结石。排除标准：凝血功能障碍；严重心肺脑疾病；孤立性肾结石或完全型鹿角形结石；肾脏位置或解剖结构异常；二期碎石、取石。106 例患者随机分为对照组和研究组，各 53 例，对照组年龄 31~72 岁，平均（53.28± 5.11）岁；男 32 例，女 21 例；右侧重度肾积水 24 例，左侧重度肾积水 29 例；结石直径（1.98± 0.27）cm；病程（1.47± 0.16）年。研究组年龄 32~74 岁，平均（54.26± 4.39）岁；男 35 例，女 18 例；右侧重度肾积水 30 例，左侧重度肾积水 23 例；结石直径（1.94± 0.29）cm；病程（1.43± 0.18）年。两组基线资料比较无统计学差异（P>0.05）。

1.2 方法

对照组采用输尿管镜取石术治疗，患者为膀胱截石位，予以连续硬膜外麻醉。用输尿管镜，通过尿道于输尿管斑马导丝或导管引导下于患侧输尿管置入输尿管镜管至结石下方，在监视器指导下结合激光技术碎石，经灌洗后冲洗结石，取钳夹将较大结石取出，术后常规留置双 J 管。

研究组采用 RPLU 术治疗，患者气管插管全身麻醉，取健侧卧位，将肾区垫高，抬高腰桥。于腋后线和 12 肋缘下取与肋缘平行的 2 cm 切口，将各层肌肉、腰背筋膜钝性分离，推开腹膜。放置自制水囊，注水 300 mL 创建后腹腔，于手指引导下截髂嵴上方 2 cm 创建 10 mm Troca，于腋前线肋缘下创建 5 mm Troca，将腋后线切口缝合，置入 10 mm Troca，并不断注入二氧化碳气体。以肾下极及腰大肌为标志，将肾周筋膜切开，使肾下极游离，明确输尿管并纵行切开，将结石取出，输尿管内放置双 J 管，取微桥将输尿管缝合。两组术后均进行常规抗感染处理，术后 4~5 周复查肾 - 输尿管 - 膀胱摄影，将双 J 管拔除。

1.3 观察指标

记录两组手术时间、术中出血量、术后排气时间、住院时间及结石清除率[9]（术后 1~2 d 复查 KUB，结石直径 <0.4 cm 或无结石残余，无需特殊干预，判定为结石清除；结石直径≥ 0.5 cm 需进行体外冲击波碎石或药物排石），并观察两组患者并发症发生情况。

于术前 24 h 及术后 24 h 检测采集两组患者外周静脉血，测定血红蛋白水平。于术前及术后 3 个月采集患者外周静脉血，用全自动生化分析仪测定血肌酐及血尿酸氮水平。于术前及术后 7 d 采集患者晨起尿液，用酶联免疫分析法测定尿内皮素 -1（ET-1）、水通道蛋白 -1（AQP-1）、单核细胞趋化蛋白 -1（MCP-1）水平。

1.4 统计学分析

数据处理选用 SPSS18.0 软件包，计量资料用（$\bar{x}\pm s$）表示，选用 t 检验，计数资料用[例（%）]表示，用 x^2 检验比较，P<0.05 表示差异有统计学意义。

2 结果

2.1 两组手术指标分析

研究组手术时间及住院时间多于对照组，结石清除率高于对照组，比较有统计学差异（P<0.05）；两组术中出血量、术后排气时间比较无统计学差异（P>0.05），见表 1。

表 1 两组手术指标分析[（$\bar{x}\pm s$），（例，%）]

Table 1 Analysis of surgical indexes of two groups[（$\bar{x}\pm s$），（n,%）]

Groups	n	Operation time (min)	Intraoperative blood loss (mL)	Postoperative exhaust time (d)	hospitalization time (d)	Stone clearance rate (%)
Control group	53	44.05± 5.01	34.28± 4.75	1.12± 0.11	4.29± 0.51	49 (92.45)
Research group	53	74.18± 9.23#	36.04± 4.21	1.04± 0.14	6.24± 0.83#	53 (100.00)#

Note: vs control group, #P<0.05.

2.2 两组血红蛋白分析

术前，两组血红蛋白比较无统计学差异（P>0.05）；术后，两组血红蛋白较术前无显著差异（P>0.05），见表 2。

2.3 两组肾功能分析

术前，两组肾功能比较无统计学差异（P>0.05）；术后，两组血肌酐及血尿酸氮均下降，两组比较无统计学差异（P>0.05），见表 3。

2.4 两组尿 ET-1、AQP-1、MCP-1 水平分析

术前，两组尿 ET-1、AQP-1、MCP-1 水平比较无统计学差异（P>0.05）；术后，两组尿 ET-1、AQP-1、MCP-1 水平均下降，两组比较无统计学差异（P>0.05），见表 4。

表 2 两组血红蛋白分析($\bar{x}\pm s$)

Table 2 Analysis of hemoglobin of two groups($\bar{x}\pm s$)

Groups	n	Time	Hemoglobin(g/L)
Control group	53	Preoperative	127.95± 14.09
		Postoperative	123.03± 15.01
Research group	53	Preoperative	125.44± 14.84
		Postoperative	120.76± 15.38

表 3 两组肾功能分析($\bar{x}\pm s$)

Table 3 Analysis of renal function of two groups($\bar{x}\pm s$)

Groups	n	Time	Serum creatinine(μmol/L)	Blood urea nitrogen (mmol/L)
Control group	53	Preoperative	160.19± 20.17	14.30± 1.29
		Postoperative	93.27± 14.29*	6.42± 0.68*
Research group	53	Preoperative	165.03± 22.08	14.01± 1.43
		Postoperative	96.41± 12.15*	6.87± 0.61*

vs the same group before operation, *P<0.05.

表 4 两组尿 ET-1、AQP-1、MCP-1 水平分析($\bar{x}\pm s$)

Table 4 Analysis of urine ET-1, AQP-1, MCP-1 levels of two groups($\bar{x}\pm s$)

Groups	n	Time	ET-1(ng/L)	AQP-1(ng/L)	MCP-1(ng/L)
Control group	53	Preoperative	67.01± 8.03	34.49± 5.01	486.05± 61.85
		Postoperative	16.33± 2.01*	31.24± 3.62*	337.14± 39.04*
Research group	53	Preoperative	64.98± 8.95	35.18± 4.27	480.12± 64.27
		Postoperative	15.97± 2.47*	31.01± 3.85*	330.55± 41.29*

vs the same group before operation, *P<0.05.

2.5 两组手术并发症分析

两组并发症总发生率比较无统计学差异(P>0.05),见表 5。

表 5 两组手术并发症分析(例,%)

Table 5 Analysis of surgical complications of two groups(n,%)

Groups	n	Mild hydronephrosis	Fever	Total incidence rate
Control group	53	4(7.55)	3(5.66)	7(13.21)
Research group	53	3(5.66)	1(1.89)	4(7.55)

3 讨论

上尿路结石为泌尿外科的多发疾病,近年来我国上尿路结石的发生率呈明显增加趋势[10,11]。上尿路结石长期梗阻可引起肾脏积水,导致肾皮质变薄,使肾功能损伤。手术治疗原则在于解除梗阻,减轻患者症状,防止肾功能进一步恶化,提高生活质量。传统切开取石术虽可有效清除结石,但创伤大,疼痛明显,有一定局限性[12]。

近年来上尿路结石的治疗以微创方式为主,尽管体外震波碎石是既往治疗上尿路结石的有效、安全手段,但对于体积较大及合并重度肾积水者的排石率明显降低, 且排石过程较长,疗效不甚理想[13,14]。输尿管镜取石术可在输尿管镜引导下的精确取石,其可明显减少并发症,减轻患者痛苦。但有研究认为[15],对于结石质地较硬、直径较大者,其手术较长,结石容易反流移位,残石率较高,需再次进行体外震波碎石术。

经腹腹腔镜输尿管切开取石术的操作简单, 视野清晰,易辨认组织,且可同时处理两侧结石,但对腹腔脏器的影响较大,不利于术后胃肠功能的恢复[16]。RPLU 术为最新发展的治疗上尿路结石手段,其不进入腹腔,对胃肠道的影响小,术后肠梗阻、肠粘连等并发症的风险较小,且可避免尿性腹膜炎的发生[17]。RPLU 术的手术径路和目标较近,无须切断肌肉,可尽快发现结石,其取石较彻底,无结石残留,能够一次取净结石,无需再次或多次手术取石[18]。RPLU 术能够降低感染扩散风险,无需一期经皮肾造瘘。既往研究报道[19],RPLU 术操作和开放取石术接近,侧卧位下暴露输尿管和肾,但较开放手术治疗上尿路结石具有创伤轻、切口小及并发症少等特点。

临床研究表明[20],RPLU 术中解剖标志欠清晰,操作空间较小,且有一定难度,可能延长手术时间。本研究结果显示,RPLU 术组手术时间较长, 与研究报道结果相符。进一步分析显示, RPLU 术组术中出血量、术后排气时间输尿管镜取石术组相似, 证实 RPLU 术在重度肾积水的上尿路结石中的微创优势。有研究表明[21],输尿管结石体积较大,病程较长,手术难度较大,难以通过一次性手术清除。本研究数据显示,RPLU 术后结石清除率为 100%,无结石残留,输尿管镜组结石清除率相对较低,证实 RPLU 术在重度肾积水的上尿路结石中的效果。另外本研究发现,两组术后血红蛋白无显著差异,说明两种术式失血量相似。

相关研究报道[22],上尿路结石产生梗阻后能够增加肾盂及肾盏压力,导致肾实质变薄,降低肾血流速度,加重肾积水程度,影响肾功能。手术是治疗重度肾积水的上尿路结石的主要手段,能够解除梗阻,为肾功能恢复提供有利条件[23]。本研究结果显示,两组术后血肌酐、尿素氮均较术前下降,组间无显著差异,提示两种术式均可改善肾功能,考虑与其均可有效清除结石,解除尿路梗阻有关。

肾脏为机体重要脏器,可通过尿液生成维持机体内环境的相对稳定,尿液中有较多的生物学标志物,能够反映机体脏器的功能状态[24]。另外尿液标本的采集简便,且无创伤,可重复取样。ET-1 的血管收缩作用已得到临床研究证实,近年来有研究报道 [25,26],ET-1 能够参与输尿管梗阻后肾血管及肾功能调节。ET-1 还可诱导细胞生长增殖,影响肾小管的水钠重吸收。据有关文献指出,积水肾盂中 ET-1 表达相对较高,动物模型也表明[27,28],输尿管梗阻小鼠 ET-1 浓度显著上升,是细胞及血管损伤的重要介质。AQP-1 为重要的膜通道,是水进出细胞的主要途径,对甘油或水渗透的选择性高,在保持细胞内环境温度平衡中有重要作用。相关研究发现[29],渗透梯度环境下,AQP-1 可诱导水分子快速通过细胞膜,参与体温调节、肾对水的重吸收等作用。研究表明[30],AQP-1 在尿液浓缩及肾脏近曲效果等重吸收中有重要作用,输尿管梗阻解除后 AQP-1 水平显著下降。Patil R V 等[31,32]通过研究也发现,小鼠敲除 AQP-1 基因后能够明显增加饮水量及尿液量。临床研究也证实,AQP1 可由肾小管上皮细胞分泌至机体尿液中,同时尿中 AQP1 和 AQP1 在肾脏细胞膜上的表达为正相关。另有研究报道,随着输尿管长时间梗阻,肾盂压力不断增加,导致肾小球上皮细胞损伤,刺激 MCP-1 表达[34]。肾积水动物模型报道[35],小鼠尿液中 MCP-1 表达显著上升, 并表明 MCP-1 在输尿管梗阻所致肾积水肾功能损伤中有重要作用。MCP-1 为单核细胞的趋化、活化因子,能够激活特异性的趋化因子,产生活性氮、活性氧及蛋白激酶等,对肾脏产生损伤。Hosaka 等[36]研究也认为,MCP-1 水平和肾积水及肾功能损伤程度有直接关联。本研究结果显示,两组术后尿 ET-1、AQP- 及 MCP-1 水平均降低,组间无显著差异,提示上尿路结石梗阻解除后能够下调相关细胞因子的表达,从而可能改善患者肾积水情况。两组患者均有少数轻度积水发生,可能原因为患者术前肾积水程度较重,导致肾皮质变薄,梗阻解除后降低肾内压力和肾脏排泄功能,使患者发生轻度肾积水。另外两组术后有少数患者发生皮下气肿发生,组间发生率无显著差异。

综上所述,RPLU 术是治疗重度肾积水的上尿路结石清除率高,创伤小,可作为重度肾积水伴上尿路结石安全、有效的术式。尽管 RPLU 术在重度肾积水的上尿路结石中的效果可靠,但临床仍应严格把握手术适应症,提高临床效果。

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