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## 兔前交叉韧带损伤后膝关节本体感觉、残端血运 及膝关节腔尿激酶型纤溶酶原激活物变化的实验研究\*

邢叔星 黄 强 李正疆 班照楠 何 欣 钟 航 曹万全 吉海波 吴昭君

(成都市第五人民医院骨科 四川 成都 611130)

**摘要** 目的:研究兔前交叉韧带(ACL)损伤后膝关节本体感觉、残端血运及膝关节腔尿激酶型纤溶酶原激活物(u-PA)的变化情况。方法:选取 80 只新西兰兔进行研究,将其以随机数字表法分作模型组及空白对照组各 40 只。模型组建立单侧 ACL 损伤模型,空白对照组仅切开关节。比较两组术前及术后 2 周、4 周、8 周时膝关节本体感觉、残端血运及膝关节腔 u-PA 水平的差异。结果:模型组新西兰兔术后 2 周、4 周、8 周时的体感诱发电位(SEP)、肌电图(EMG)潜伏期均高于空白对照组,而 SEP、EMG 波幅均低于空白对照组 ( $P<0.05$ )。模型组新西兰兔术后 2 周、4 周、8 周时的残端组织微血管密度分别为  $(2.04\pm 0.24)\text{n/mm}^2$ 、 $(2.75\pm 0.61)\text{n/mm}^2$ 、 $(1.60\pm 0.33)\text{n/mm}^2$ ,均高于空白对照组的  $(1.34\pm 0.24)\text{n/mm}^2$ 、 $(1.34\pm 0.25)\text{n/mm}^2$ 、 $(1.35\pm 0.26)\text{n/mm}^2$ ,差异均有统计学意义( $P<0.05$ )。模型组新西兰兔术后 2 周、4 周、8 周时的膝关节液 u-PA 水平分别为  $(173.97\pm 14.29)\text{pg/mL}$ 、 $(188.37\pm 15.82)\text{pg/mL}$ 、 $(171.38\pm 14.76)\text{pg/mL}$ ,均高于空白对照组的  $(158.02\pm 10.18)\text{pg/mL}$ 、 $(157.68\pm 10.20)\text{pg/mL}$ 、 $(157.37\pm 10.07)\text{pg/mL}$ ,差异均有统计学意义( $P<0.05$ )。结论:ACL 损伤后会在不同程度上影响膝关节本体感觉、残端血运及膝关节腔 u-PA 含量,值得临床进一步研究。

**关键词:**前交叉韧带;膝关节本体感觉;残端血运;尿激酶型纤溶酶原激活物

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## Experimental Study on Changes of Knee Proprioception, Stump Blood Supply and Urokinase-Type Plasminogen Activator in the Knee Cavity after Anterior Cruciate Ligament Injury in Rabbit\*

XING Shu-xing, HUANG Qiang, LI Zheng-jiang, BAN Zhao-nan, HE Xin, ZHONG Hang, CAO Wan-quan, JI Hai-bo, WU Zhao-jun  
(Department of Orthopaedics, Chengdu Fifth People's Hospital, Chengdu, Sichuan, 611130, China)

**ABSTRACT Objective:** To study the changes of knee proprioception, stump blood supply and urokinase-type plasminogen activator (u-PA) in the knee cavity after anterior cruciate ligament (ACL) injury in rabbits. **Methods:** 80 New Zealand rabbits were selected for the study, and they were divided into model group and blank control group with 40 rabbits each by random number table method. A unilateral ACL injury model was established in the model group, and only the joint was cut open in the blank control group. The knee proprioception, stump blood supply and u-PA level in the knee cavity were compared between the two groups before and 2, 4 and 8 weeks after operation. **Results:** The incubation period of somatosensory evoked potential (SEP) and electromyography (EMG) in the model group were higher than those in the blank control group at 2, 4 and 8 weeks after operation, while the amplitude of SEP and EMG were lower than those in the blank control group ( $P<0.05$ ). The microvessel density of stump tissue in the model group at 2, 4 and 8 weeks after operation were  $(2.04\pm 0.24)\text{n/mm}^2$ ,  $(2.75\pm 0.61)\text{n/mm}^2$  and  $(1.60\pm 0.33)\text{n/mm}^2$  respectively, which were higher than those in the blank control group  $(1.34\pm 0.24)\text{n/mm}^2$ ,  $(1.34\pm 0.25)\text{n/mm}^2$ ,  $(1.35\pm 0.26)\text{n/mm}^2$ , the differences were statistically significant ( $P<0.05$ ). The u-PA level of articular fluid in the model group at 2, 4 and 8 weeks after operation were  $(173.97\pm 14.29)\text{pg/mL}$ ,  $(188.37\pm 15.82)\text{pg/mL}$ ,  $(168.38\pm 14.76)\text{pg/mL}$  respectively, which were higher than those in blank control group  $(158.02\pm 10.18)\text{pg/mL}$ ,  $(157.68\pm 10.20)\text{pg/mL}$ ,  $(157.37\pm 10.07)\text{pg/mL}$ , the differences were statistically significant ( $P<0.05$ ). **Conclusion:** After ACL injury, the knee proprioception, stump blood supply and u-PA content in the knee cavity can be affected to different degrees, which is worthy of further clinical study.

**Key words:** Anterior cruciate ligament; Knee proprioception; Stump blood supply; Urokinase-type plasminogen activator

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作者简介:邢叔星(1975-),男,博士,主任医师,从事关节及运动医学方面的研究,E-mail: zhangxing20130720@163.com

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## 前言

前交叉韧带(ACL)属于膝关节的重要稳定结构,主要作用体现在抑制膝关节胫骨前移和旋转荷载等方面,从而提供机械稳定性<sup>[1-3]</sup>。与此同时,ACL具备本体感觉,可通过神经反射途径实现对肌肉收缩的控制,从而保证躯体处于平衡状态,避免损伤的发生。ACL损伤会导致膝关节不稳,大幅增加半月板损伤以及软骨过度磨损的风险<sup>[4-6]</sup>,因此如何有效治疗 ACL 损伤显得尤为重要,亦是临床研究中的热点之一。此外,ACL 损伤之后其力学强度明显下降,但残存韧带结构仍和股骨、胫骨相连,继而导致韧带内保留的本体感受器仍可继续受到机械刺激。在上述状况下 ACL 是否仍可发挥本体感觉功能尚且存在一定的争议。另外,尿激酶型纤溶酶原激活物(u-PA)在纤维蛋白组织形成过程中发挥着至关重要的作用,且和炎症反应及基质降解等多种病理过程密切相关<sup>[7-9]</sup>。然而,关于 ACL 损伤后膝关节腔内 u-PA 变化情况尚未彻底阐明。鉴于此,本文通过研究兔 ACL 损伤后膝关节本体感觉、残端血运及膝关节腔 u-PA 的变化情况,旨在为后续的临床研究提供数据支持,现作以下报道。

## 1 材料与方法

### 1.1 动物

选取 80 只新西兰兔进行研究,体质量为 270~330 g,雌雄各半,均购自中国科学院上海药物研究所实验动物中心,动物许可证号:SCXK(沪)2020-1228,伦理批号:2020654。采用标准饲料喂养,自由饮水、摄食,饲养环境为多层层流架,温度维持在 20~25℃,湿度 50~70%,12 h 昼夜循环照明(08:00~20:00),适应性喂养 2 周。

### 1.2 试剂

兔 u-PA 酶联免疫吸附试验(ELISA)试剂盒(购自上海江莱生物科技有限公司)。

### 1.3 仪器

Multiskan FC 酶标仪(购自美国赛默飞世尔公司),BL-420F 生物机能实验系统(购自上海益联医学仪器发展有限公司),FV3000 激光扫描共聚焦显微镜(购自日本奥林巴斯株式会社)。

### 1.4 方法

将 80 只新西兰兔以随机数字表法分作模型组及空白对照组各 40 只。模型组新西兰兔实施单侧 ACL 横断处理,即在麻醉起效之后,常规消毒铺巾,作一膝前正中切口,对内侧的支持带实施切开处理,脱位髌骨,暴露关节腔。随后于 ACL 实质部将其彻底横断并作 2 mm 的缺损,冲洗关节腔,逐层缝合,最后关闭切口。术后常规予以抗生素干预,患肢不予以固定处理,正常饮食,不限制活动。空白对照组仅切开关节,不做任何后续处理,直接关闭切口,术后处理和模型组一致。

### 1.5 观察指标

(1)膝关节本体感觉检测:包括体感诱发电位(SEP)、肌电图(EMG)。① SEP:首先对新西兰兔实施局部麻醉并妥善固定,经原手术切口进入膝关节,充分暴露 ACL。所记录电势放在两眼眶最后连线和正中矢状方向朝后 5 mm,再朝右 2 mm。选择鼻根处置入皮层参考电极,下肢近心端置入接地电极。于 27℃

条件下完成 SEP 测定,通过双极表面电极于 ACL 两极近骨处实施电刺激,最后以 BL-420F 生物机能实验系统完成新西兰兔 SEP 的记录。② EMG:麻醉及操作方式和 SEP 相同,借助刺激电极对 ALC 进行刺激,选择腓绳肌肌腹置入记录电极,同侧肢体踝置入参考电极,刺激参数为恒压、3Hz、19V、0.1 ms。通过上述系统完成新西兰兔 EMG 的记录,将电流刺激结果传输至相关计算软件中,完成 EMG 潜伏期、波幅的计算。(2)残端血运检测:检测指标为残端组织微血管密度,两组均分别于术前、术后 2 周、术后 4 周及术后 8 周时各处死 10 只新西兰兔,顺着髌骨旁内侧缘切一 3 cm 左右的切口,分离皮下组织。切关节囊,将髌骨缓慢朝外侧翻开,屈曲膝关节,以手术刀将 ACL 残端自胫骨端实施切断处理,放置在 10%多聚甲醛内固定备用。常规制片、脱蜡、染色处理,随后放置于显微镜下完成微血管密度的测定。首先于低倍镜下选择微血管数密度最高的区域,随后更换高倍镜采集图像。将所获取的图像传输至 Image-Pro Plus 6.0 图像分析系统并完成微血管计数。采用该图像分析系统将图片标记比例尺,计算图像实际面积,最后完成微血管密度的计算。(3)关节液 u-PA 水平检测:分别于术前及术后 2、4、8 周时采集两组新西兰兔的关节液 3 mL,以 2500 r/min 作为离心速率进行时长 20 min 的离心处理,并以 ELISA 完成检测,操作遵循试剂盒说明书完成。

### 1.6 统计学处理

使用 SPSS23.0 进行研究资料分析。研究资料主要为重复测量计量数据,均通过正态性检验,以均值  $\bar{x} \pm SD$  描述,统计处理为重复测量方差分析(统计量为 F)+ 两两间比较 LSD-t 检验(统计量为 LSD-t)+ 两两时间比较差值 t 检验(统计量为 t)。统计检验水准  $\alpha=0.05$ ,两两时间比较差值 t 检验涉及多次比较按 Bonferroni 校正法进行检验水准调整。

## 2 结果

### 2.1 两组新西兰兔 SEP、EMG 的潜伏期及波幅对比

模型组新西兰兔术后 2 周、4 周、8 周时的 SEP、EMG 潜伏期均高于空白对照组,而 SEP、EMG 波幅均低于空白对照组( $P<0.05$ )。见表 1。

### 2.2 两组新西兰兔损伤前后残端组织微血管密度对比

模型组新西兰兔术后 2 周、4 周、8 周时的残端组织微血管密度均高于空白对照组(均  $P<0.05$ )。见表 2。

### 2.3 两组新西兰兔损伤前后关节液 u-PA 水平对比

模型组新西兰兔术后 2 周、4 周、8 周时的关节液 u-PA 水平均高于空白对照组(均  $P<0.05$ )。见表 3。

## 3 讨论

随着近年来人们生活方式的日益改变以及人们对生活品质的追求逐渐提升,运动损伤和车祸伤的发生率呈逐年攀升趋势,从而导致 ACL 损伤发生率增高<sup>[10-12]</sup>。ACL 损伤后,会对患者膝关节运动功能产生极大程度的影响,甚至促使其丧失运动的能力。国内一项有关运动员 ACL 的报道发现,约有 0.47% 的运动员有 ACL 损伤史,已在相关领域引起一定的关注度<sup>[13]</sup>。伴随着医疗模式的不断转变,目前临床上针对 ACL 损伤的治疗目标已从既往的单纯重视膝关节生物力学稳定性恢复,逐渐向肢

表 1 两组新西兰兔 SEP、EMG 的潜伏期及波幅对比( $\bar{x} \pm s$ )

Table 1 Comparison of latency and amplitude of SEP and EMG in two groups of New Zealand rabbits( $\bar{x} \pm s$ )

| Groups                      | Time                    | SEP                       |                           | EMG                       |                          |
|-----------------------------|-------------------------|---------------------------|---------------------------|---------------------------|--------------------------|
|                             |                         | Incubation period( ms )   | Amplitude( uV )           | Incubation period( ms )   | Amplitude( uV )          |
| Blank control group( n=40 ) | Before operation        | 15.25± 2.25               | 21.15± 2.91               | 6.05± 0.61                | 0.50± 0.03               |
|                             | 2 weeks after operation | 15.04± 2.19               | 21.28± 2.87               | 6.15± 0.60                | 0.51± 0.04               |
|                             | 4 weeks after operation | 15.33± 2.14               | 21.05± 2.83               | 6.23± 0.62                | 0.50± 0.03               |
|                             | 8 weeks after operation | 14.80± 2.08               | 20.74± 2.77               | 6.18± 0.61                | 0.52± 0.04 <sup>†</sup>  |
| Model group( n=40 )         | Before operation        | 15.01± 2.12               | 20.97± 3.11               | 6.21± 0.62                | 0.50± 0.03               |
|                             | 2 weeks after operation | 22.39± 3.26 <sup>at</sup> | 13.76± 2.58 <sup>at</sup> | 13.41± 1.66 <sup>at</sup> | 0.36± 0.02 <sup>at</sup> |
|                             | 4 weeks after operation | 28.97± 3.64 <sup>at</sup> | 12.45± 2.24 <sup>at</sup> | 15.89± 1.96 <sup>at</sup> | 0.22± 0.01 <sup>at</sup> |
|                             | 8 weeks after operation | 21.41± 2.92 <sup>at</sup> | 14.20± 2.63 <sup>at</sup> | 12.50± 1.78 <sup>at</sup> | 0.34± 0.01 <sup>at</sup> |
| Overall analysis            | HF coefficient          | 0.6529                    | 0.8444                    | 0.5048                    | 0.4508                   |
| Comparison between groups   | F, P                    | 434.525, 0.000            | 343.170, 0.000            | 1,641.405, 0.000          | 2,492.099, 0.000         |
| Intra group comparison      | F, P                    | 103.434, 0.000            | 39.722, 0.000             | 254.675, 0.000            | 294.715, 0.000           |
| Interaction                 | F, P                    | 100.383, 0.000            | 37.716, 0.000             | 237.395, 0.000            | 309.275, 0.000           |

Note: Compared with blank control group, <sup>a</sup> $P < 0.05$ ; compared with before operation, <sup>†</sup> $P < 0.05$ .

表 2 两组新西兰兔损伤前后残端组织微血管密度对比( $n/mm^2$ ,  $\bar{x} \pm s$ )

Table 2 Comparison of microvessel density of stump tissue between two groups before and after operation( $n/mm^2$ ,  $\bar{x} \pm s$ )

| Groups                      | Time                    | Microvessel density of stump tissue |
|-----------------------------|-------------------------|-------------------------------------|
| Blank control group( n=10 ) | Before operation        | 1.35± 0.24                          |
|                             | 2 weeks after operation | 1.36± 0.25                          |
|                             | 4 weeks after operation | 1.34± 0.26                          |
|                             | 8 weeks after operation | 1.36± 0.25                          |
| Model group( n=10 )         | Before operation        | 1.32± 0.23                          |
|                             | 2 weeks after operation | 2.02± 0.25 <sup>at</sup>            |
|                             | 4 weeks after operation | 2.75± 0.65 <sup>at</sup>            |
|                             | 8 weeks after operation | 1.59± 0.34 <sup>†</sup>             |
| Overall analysis            | HF coefficient          | 0.6691                              |
| Comparison between groups   | F, P                    | 84.283, 0.000                       |
| Intra group comparison      | F, P                    | 15.274, 0.000                       |
| Interaction                 | F, P                    | 15.871, 0.000                       |

Note: Compared with blank control group, <sup>a</sup> $P < 0.05$ ; compared with before operation, <sup>†</sup> $P < 0.05$ .

体感觉功能恢复的方向侧重,以期获得更为理想的治疗效果,使 ACL 损伤患者能更好的回归正常工作生活<sup>[14-16]</sup>。ACL 损伤后对膝关节本体功能、韧带内机械感受器和肢体感觉的影响是当下研究的热点<sup>[17-19]</sup>,亦是针对 ACL 损伤患者制定更为合理有效治疗方案的重要参考,具有较为积极的临床意义。

本文结果发现,模型组新西兰兔术后 2 周、4 周、8 周时的 SEP、EMG 潜伏期均高于空白对照组,而 SEP、EMG 波幅均低于空白对照组。这在既往相关研究中得以佐证<sup>[20]</sup>,提示了 ACL 损伤后膝关节本体感觉明显下降。考虑原因,ACL 损伤发生后,由于关节内环境的特殊性,易导致其无法自行愈合,且 ACL 损伤发生后患者韧带强度势必受到一定程度的影响,继而易出现

逐渐松弛的状况,进一步导致韧带内机械感受器难以接受到适当刺激,最终导致关节本体感受出现下降<sup>[21-23]</sup>。同时,ACL 损伤后患者还会出现躯干姿势控制能力降低的情况,究其原因,ACL 损伤后肢体传入中神经系统的信号会发生改变,从而影响中枢神经系统对肢体协调以及肌肉控制的功能,最终促使肢体稳定性发生异常改变<sup>[24-26]</sup>。此外,本研究结果显示模型组新西兰兔术后 2 周、4 周、8 周时的残端组织微血管密度均高于空白对照组,且模型组新西兰兔术后 4 周的残端组织微血管密度最高。这提示了 ACL 损伤后膝关节残端血运随时间变化差异明显,临床实际工作中应合理选择血运最丰富的时候实施重建,以提高重建效果以及改善预后<sup>[27-29]</sup>。另外,本研究显示,模型

表 3 两组新西兰兔损伤前后关节液 u-PA 水平对比 (pg/mL,  $\bar{x} \pm s$ )Table 3 Comparison of u-PA level in articular fluid between the two groups of New Zealand rabbits before and after operation (pg/mL,  $\bar{x} \pm s$ )

| Groups                     | Time                    | u-PA level in articular fluid   |
|----------------------------|-------------------------|---------------------------------|
| Blank control group (n=10) | Before operation        | 158.06 $\pm$ 10.33              |
|                            | 2 weeks after operation | 158.65 $\pm$ 10.90              |
|                            | 4 weeks after operation | 159.58 $\pm$ 9.80               |
|                            | 8 weeks after operation | 156.50 $\pm$ 9.50               |
| Model group (n=10)         | Before operation        | 157.74 $\pm$ 9.73               |
|                            | 2 weeks after operation | 171.31 $\pm$ 14.02 <sup>a</sup> |
|                            | 4 weeks after operation | 189.94 $\pm$ 16.50 <sup>a</sup> |
|                            | 8 weeks after operation | 172.03 $\pm$ 14.13 <sup>a</sup> |
| Overall analysis           | HF coefficient          | 0.9498                          |
| Comparison between groups  | F, P                    | 122.650, 0.000                  |
| Intra group comparison     | F, P                    | 25.880, 0.000                   |
| Interaction                | F, P                    | 21.165, 0.000                   |

Note: Compared with blank control group, <sup>a</sup> $P < 0.05$ ; compared with before operation, <sup>P</sup> $P < 0.05$

组新西兰兔术后 2 周、4 周、8 周时的关节液 u-PA 水平均高于空白对照组。这提示了 ACL 损伤后会促进膝关节腔 u-PA 水平的异常升高。其中主要原因可能在于:在疾病以及损伤等病理状态下,膝关节腔微环境的 u-PA 水平增高,并会继续促进关节腔内化膜组织的大量增生以及炎性细胞增多,并形成恶性循环。有研究学者发现<sup>[30]</sup>,u-PA 参与的细胞外基质蛋白裂解作用和骨关节炎的关节软骨破坏密切相关。另有研究报道发现<sup>[31]</sup>,类风湿性关节炎患者的血浆以及关节液中的 u-PA 含量异常升高。膝关节创伤性损伤后关节液内的 u-PA 水平显著升高<sup>[32]</sup>。上述研究结果均证实了在损伤状态下关节腔的 u-PA 水平增高,且和关节破坏以及疾病进展联系紧密。

综上所述,ACL 损伤后会在不同程度上对膝关节本体感觉、残端血运造成负面影响,同时提高关节腔内的 u-PA 水平,临床上应予以重点关注。

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