doi: 10.13241/j.cnki.pmb.2017.10.002

一种改良大鼠慢性脊髓压迫模型的建立与评价 *

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摘要 目的：在已有脊髓压迫建模方式基础上，建立一种更好模拟慢性发病的颈脊髓压迫动物模型，并对其神经功能进行初步评价。**方法：**将 20 只 SD 大鼠随机分为模型组、对照组。采用聚氨酯薄膜包裹吸水膨胀性材料聚乙烯醇构建改良慢性膨胀物大鼠脊髓损伤模型，观察不同时间点大鼠行为学运动功能（Basso, Beattie&Bresnahan locomotor rating scale, BBB scale）评分；苏木精 - 伊红（hematoxylin-eosin，HE）染色观察脊髓组织形态变化；脱氧核糖核苷酸末端转移酶介导的缺口末端标记法（TdT-mediated dUTP nick end labeling，TUNEL）检测损伤段脊髓组织细胞凋亡情况。**结果：**手术后模型组大鼠的 BBB 评分逐渐降低，模型组大鼠各时间点 BBB 评分均明显低于对照组，且两组差异具有统计学意义(P<0.05)。HE 染色见模型组大鼠较对照组有明显的组织损伤反应。TUNEL 染色显示模型组大鼠凋亡细胞明显增多。**结论：**本研究成功制备了稳定可靠、操作简单的一种改良慢性脊髓压迫模型。

关键词：慢性脊髓压迫；动物模型；聚乙烯水凝胶

中图分类号：R-33; R651.2 **文献标识码：**A **文章编号：**1673-6273(2017)10-1806-04

Establishment and Evaluation of a Modified Rat Model of Chronic Spinal Cord Compression*

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ABSTRACT Objective: To establish a better simulation of the chronic disease animal model of cervical spinal cord compression on the basis of the existing spinal cord compression model, and to evaluate its neurological function. **Methods:** Twenty SD rats were randomly divided into two groups: control group and model group. A water swelling material polyvinyl alcohol with the size of 3.0 mm*1.5mm*0.7mm was wrapped with polyurethane film, which expanded over time to induce chronic compression in the spinal cord. In the model groups, the expanding compression material was inserted between the C5 and C6 laminae and dura, resulting in chronic spinal cord compressing. The same surgery were done in the control group except for the implanting of the water-swellable compression material. Basso Beattie Bresnahan (BBB) locomotor rating scale was used at different time points to evaluate rats' hind limb motor function. Hematoxylin-eosin (HE) staining was used to observe spinal cord tissue morphology. Terminal deoxynucleotide transferase-mediated dUTP nick end labeling (TUNEL) assay was used to test the spinal cord injury tissue apoptosis. **Results:** BBB score of the model group decreased gradually after the operation, and was significantly lower than that of the control operation group at each time point, the differences between the two groups were statistically significant(P<0.05). HE staining indicated that model group rats had significant tissue response to injury compared with control group. Pathological examination of the model group revealed spinal cord damage with the formation of cavity and scar. TUNEL staining showed there were many apoptotic cells in the model group, while no apoptotic cells were found in the control operation groups. **Conclusion:** The chronic spinal cord injury model established in this study has good reproducibility and stability, can be used in the study of chronic spinal cord injury.

Key words: Chronic spinal cord compression; Animal model; Polyethylene hydrogel

Chinese Library Classification(CLC): R-33; R651.2 Document code: A

Article ID: 1673-6273(2017)10-1806-04

前言

慢性压迫是引起脊髓慢性损伤最常见的原因[1]。脊柱外科多种常见疾病均可引起脊髓的慢性进行性压迫，如椎间盘突出、脊柱肿瘤、脊柱结核、黄韧带骨化增生等，造成脊髓不同程度的损伤，进而引起相应部位运动和感觉功能障碍[2]。但由于疾病时程长、相关脊髓标本很难获取等原因，目前对于此类疾病的细胞分子水平改变以及病理生理机制尚不明确，出现瘫痪症状后的治疗也十分困难。

探索慢性脊髓压迫的病理机制、发现有效治疗手段，需要

* 基金项目：上海市科委博士后科研基金项目（14R21411100）

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(收稿日期：2016-11-03 接受日期：2016-11-26)

构建理想的动物模型[3]。已有的慢性脊髓压迫模型包括螺钉法、球囊法、肿瘤细胞移植法及缓慢膨胀性材料压迫法等[4-6]。本研究以传统缓慢膨胀性材料压迫法为基础，使用吸水膨胀性聚合物聚乙烯醇(polyvinyl alcohol, PVA)，并在其表面包裹一层带孔隙的聚氨酯薄膜，以减小水凝胶材料与体液的接触面积，减缓材料的膨胀速度，改良缓慢压迫脊髓模型。通过这一设计，希望建立更好模拟脊髓压迫慢性病程的大鼠模型。

1 材料与方法

1.1 脊髓压迫材料的制备

PVA 是以水为分散介质，用水溶性或亲水性化合物通过化学交联或物理交联方法制备的具有三维网络或互穿网络结构的一种高分子材料。水凝胶能吸水溶胀却又不溶解于水，且具有良好的组织相容性。本实验采用的吸水性压迫材料 PVA 凝胶由北京师范大学化学学院高分子化学与物理研究所提供，该材料在体外 37℃生理盐水中，大约 30 小时达到溶胀平衡，体积不再增加，最大膨胀体积约为干凝胶状态的 2 倍。试验中干燥状态的 PVA 凝胶切割成 3.0 mm× 1.5 mm× 0.7 mm 的细条状，环氧乙烷消毒后分装备用。实验前使用聚氨酯薄膜对材料进行包裹，完整包裹后，用内径为 0.26 mm 的 4 号注射器针头，于薄膜顶端和尾端各刺入两个针孔，用来允许少量液体缓慢渗入，以减缓聚乙烯醇水凝胶的膨胀速率。

1.2 动物模型制作

成年 SPF 级雄性 SD 大鼠 20 只，体重 250-300 g(上海交通大学附属第六人民医院实验动物中心提供)，许可证号：SCXK(沪)2004-0007。20 只大鼠随机分为两组，模型组 10 只，对照组 10 只。采用 4%水合氯醛作为麻醉剂，按照 1 mg/100 g 进行腹腔给药麻醉剂量对大鼠实施麻醉，麻醉后取俯卧位固定于实验板上。暴露颈背部，在 C5 至 C7 水平剃毛备皮，手术行无菌操作。显露 C5 至 C7 椎板，切除椎板间黄韧带，暴露硬脊膜。模型组将聚氨酯薄膜包裹的聚乙烯醇水凝胶置于大鼠 C5-C6 的椎板与硬脊膜之间。对照组的硬脊膜暴露及游离操作同模型组，但不放置压迫材料。整个手术操作过程动作轻柔，并注意观察大鼠的反应以及变化，尽量避免损伤硬脊膜造成脑脊液漏，以及避免脊髓急性损伤，逐层止血缝合。术后术后均给予庆大霉素局部滴入预防感染。两组大鼠术后放置于 37℃条件下单笼饲养。如果出现排尿功能障碍，即实行膀胱部按摩以帮助大鼠排尿，2 次 / 天直到大鼠恢复自行排尿功能为止。

1.3 行为学检查

行为学运动功能 BBB(Basso Beattie Bresnahan)评分是通过综合观察记录大鼠后肢运动功能来评定大鼠脊髓损伤情况的方法，具体操作方法为：将动物放入开口盆中，轻轻敲击盆壁，使其受到惊扰爬行，观察动物的臀、膝、踝关节行走、躯干运动及其协调情况[7]。研究中分别于术后 1-6 周内每周对实验大鼠进行 BBB 评分。此项检测由其他两名实验人员同时操作，测试时采用双盲法，两人独立观察记录，最后取均值为准。

1.4 病理标本的制作

术后第 6 周，完成行为学检测后，将模型组与对照组共 20 只大鼠过量麻醉。取两个输液瓶，分别灌入 500 mL 生理盐水和 100 mL 的 4%多聚甲醛固定液，连接好输液器并置于合适高度；大鼠麻醉后取仰卧位固定于实验板上，开胸暴露心脏及主动脉。将灌注针插入左心室并送入主动脉，保持针头位置固定，打开调节阀并剪开右心耳，使用生理盐水冲洗血液。观察到肠系膜血管及肝脏变白后，开始灌注 4%多聚甲醛固定液。待大鼠全身组织器官变硬后即取 C5-C7 段脊柱，以受压段为中心取约 10 mm 的颈髓标本，置 10%中性福尔马林溶液中固定后送病理科。石蜡包埋并切片，切片厚度约 4 μm，HE 染色。

1.5 TUNEL 检测

操作过程依据 TUNEL 荧光凋亡检测试剂盒厂商(Beyotime 公司)提供的说明书进行。将石蜡切片脱蜡并用蒸馏水冲洗，再滴加蛋白酶 K 处理 20 min，PBS 冲洗后，加入 TUNEL 检测液避光孵育 60 min，PBS 冲洗后封片。放于荧光显微镜下观察，可以检测到呈绿色荧光的凋亡细胞。

1.6 数据处理与统计学分析

实验数据使用 SPSS 13.0 进行统计学分析，使用 t 检验分析各组间的差异以及不同时间点每组内的差异，t 检验前行方差齐性检验，数值以均数± 标准差表示，$P<0.05$ 时有统计学意义。

2 结果

整个实验过程中有 1 只大鼠因麻醉意外死亡，及时重新造模补齐实验动物。其余大鼠手术切口愈合均良好，无感染。

2.1 大鼠运动功能评价

术后 6 周内定期监测大鼠爬行时下肢及躯干运动及协调情况。模型组大鼠术后逐渐出现后肢运动及尾巴抬举无力，步态异常，肢体活动协调性差等脊髓功能异常表现，其术后 1-6 周的 BBB 评分分别为 17.1、15.6、12.9、10.4、9.9 和 10.0 分。而对照组大鼠术后 1-6 周的 BBB 评分分别为 18.3、18.5、19.3、19.8、20.3 和 20.4，BBB 评分在术后 6 周内无明显波动，且每周检测的 BBB 评分均显著高于模型组。表明与对照组相比，模型组大鼠后肢运动功能逐渐降低，脊髓损伤逐渐加重。模型组和对照组大鼠每周 BBB 评分见表 1。

表 1 模型组及对照组大鼠各阶段 BBB 运动功能评分

Table 1 The BBB score of the control group and the model group

Groups	Weeks after operation					
	1w	2w	3w	4w	5w	6w
Control	18.3± 1.34	18.5± 0.71	19.3± 0.68	19.8± 0.63	20.3± 0.68	20.4± 0.70
Model	17.1± 0.74	15.6± 1.27	12.9± 1.20	10.4± 0.97	9.9± 0.57	10.0± 0.67
P value	0.023	0.000	0.000	0.000	0.000	0.000

2.2 脊髓组织学检测

脊髓石蜡切片 HE 染色如图 1 所示。对照组脊髓断面结构致密完整，白质与灰质分界清楚，"H" 形的脊髓灰质结构清晰，神经细胞存在于灰质中，可见尼氏体及神经元突起。模型组膜被结构松散，灰质白质分界不清。白质结构呈蜂窝状，胶质细胞增生。灰质内神经细胞肿胀崩解，部分细胞核消失，细胞数量减少，有许多空洞形成，脊髓中央管结构破坏。

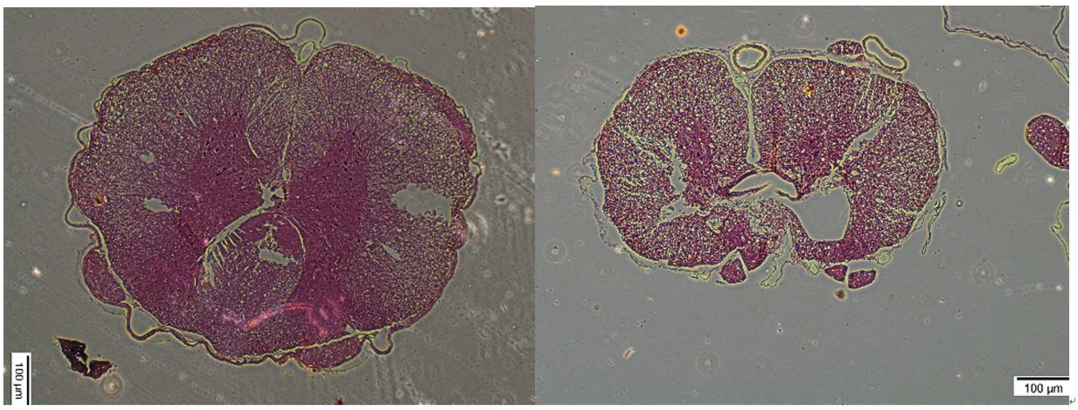

图 1 大鼠脊髓石蜡切片 HE 染色(40×)

注：左 对照组，右 模型组

Fig.1 HE staining of paraffin sections of the spinal cord in rats(40×)

Note: Left control group, right model group

2.3 凋亡细胞检测

TUNEL 检测显示对照组大鼠脊髓组织中极少发现发出绿色荧光的凋亡细胞；而模型组大鼠脊髓组织中可见到大量发出绿色荧光的 TUNEL 阳性细胞(图 2)，表明模型组大鼠脊髓组织中有明显的凋亡过程发生。

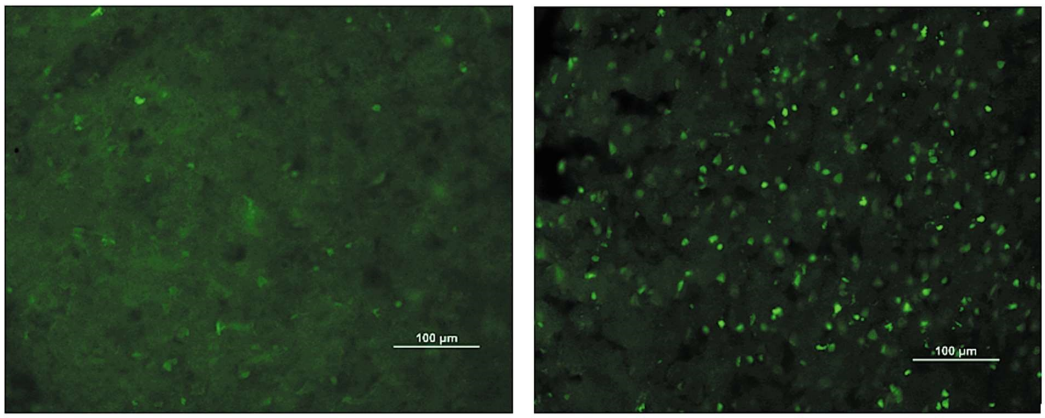

图 2 大鼠脊髓石蜡切片 TUNEL 染色(100×)

注：左 对照组，右 模型组

Fig.2 TUNEL staining of paraffin sections of spinal cord in rats (100×)

Note: Left control group, right model group

3 讨论

慢性脊髓压迫损伤一直是脊柱外科领域基础研究的热点，由于慢性脊髓压迫后的病理生理机制十分复杂，其发展过程、发病机制以及颈脊髓的病理生理变化目前尚不明确，因此建立模拟人慢性脊髓压迫发病过程的动物模型显得十分重要。

过去已建立了大量成功的脊髓损伤模型，但大部分模型属于急性损伤，如非常经典的重物坠落法[8]，该方法由 Allen 在 1911 年最先报道。其他常见的模型如钳夹型损伤模型[9-11]、全横断性及脊髓半切性脊髓损伤模型[12,13]等也同样属于急性损伤模型。急性损伤带来的脊髓理化因素损害以及继发的出血、水肿、微循环障碍等使脊髓组织压力增高、组织缺氧从而引起脊髓神经组织缺血、退变、坏死[14]，其病理生理过程与脊髓慢性压迫损伤有较大差别，因此急性脊髓损伤动物模型不适合用于研究慢性脊髓压迫。

对于慢性脊髓压迫模型的建立，众多学者对此做了大量工作。已建立的慢性压迫模型有螺钉法[15-17]、球囊法[18-20]、双套管法[21]、肿瘤细胞移植法[22]、硬化剂注射法[23]等。任何一种压迫模型

都有其自身存在的缺点。螺钉法和球囊扩张法需定时手工操作,较为繁琐;螺钉拧入需定期捉取动物并切开伤口进行操作,使得实验对象长期处于惊恐状态,且螺钉拧入时垂直用力大小影响螺钉进入深度,各实验对象之间存在差异性;球囊可向各个方向扩张,实验过程中难以控制压迫面积和压迫程度,从相关研究中可以看到该模型所得的脊髓大体标本外形以及压迫程度存在一定的差别,从而增加了组间误差;而且以上慢性脊髓压迫模型,其本质更近似于多次的急性脊髓损伤相累加,并不能很好的模拟脊髓慢性压迫的病理生理过程。肿瘤细胞移植法中肿瘤细胞生长无序,常扩散至其余节段,不能很好地控制对脊髓的压迫程度,建模成功率亦较低。

膨胀性材料压迫法模型通过手术将吸水膨胀材料植入到大鼠椎板与硬脊膜之间。既往研究表明该模型具有压迫方向、程度易于控制等特点,且材料植入动物体内后无需人为干预,减少反复的手术操作,降低模型术后的感染率和死亡[24]。本实验在既往膨胀性材料压迫模型的基础上,使用聚氨酯薄膜包裹PVA水凝胶,减小了水凝胶与周围体液的接触面积,从而使膨胀更加缓慢稳定,这有可能更好地模拟脊髓慢性压迫损伤的病理生理过程。

本实验构建的大鼠慢性脊髓压迫模型,制作相对简单、成功率高、具有较好的重复性与稳定性,是一个较为理想的动物实验模型。但实验中压迫材料从脊髓背侧植入并膨胀压迫脊髓,而临床上的慢性脊髓压迫多由椎间盘突出、韧带骨化增生等引起,其主要压迫脊髓腹侧,本实验并没有很好的模拟临床实际中的这一特点,这恰是本实验的不足之处。

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