实验性牙移动模型大鼠构建：牙齿移动后空口咀嚼时间变化规律

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文章亮点：

文章观察了不同正畸矫治力矫治条件下大鼠牙移动模型空口咀嚼时间变化，结果发现，随着正畸矫治力的增加，单位时间空口咀嚼时间增加，在相同正畸矫治力条件干预下，大鼠单位时间空口咀嚼时间变化规律和临床正畸加力后疼痛变化规律一致，并且和传统观测直接梳理面部行为学变化趋势一致。

关键词：

实验动物模型；口腔损伤及修复动物模型；实验性牙齿移动；正畸矫治力；错颌畸形；交互牵引；自发疼痛；空口咀嚼；直接梳理面部；变化规律

主题词：

组织工程；牙齿；疼痛；模型，动物

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摘要

背景：错颌畸形正畸交互牵引移动牙齿产生有规律自发性疼痛，但是疼痛的中枢神经传导通路以及疼痛的基本机制并不清楚。

目的：建立实验性牙移动模型大鼠，观察大鼠牙移动后单位时间空口咀嚼行为学变化规律。

方法：将大鼠随机分为空白组，阴性对照组和模型组，模型组使用改良Colin.K.法，用镍钛丝正畸矫治力交互牵引大鼠上颌前后牙建立大鼠牙移动模型；空白组无交互牵引装置；阴性对照组不加矫治力；分别检测在牙移动后4，12 h，移动后1，3，5，7 d大鼠空口咀嚼行为学改变；牙移动后1 d，牙齿移动分别加力30，60，90 g，观察大鼠空口咀嚼相关行为学变化。

结果与结论：与阴性对照组和空白组比较，模型组大鼠牙移动后4 h开始，空口咀嚼时间总和开始增加，牙移动后12 h空口咀嚼时间明显增加($P < 0.05$)，牙移动后1 d达到峰值($P < 0.01$)，随后缓慢下降至7 d。牙齿移动后1 d，模型组大鼠施加正畸矫治力30，60，90 g的空口咀嚼时间均差异有显著性意义($P < 0.05$)。结果证实，牙齿移动后空口咀嚼时间变化规律和临床正畸牙移动疼痛规律一致，能够作为大鼠牙移动后口颌面部疼痛相关行为学反应之一。

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Construction of rat models of experimental tooth movement: time variation of chewing-like jaw movements after tooth movement

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Abstract

BACKGROUND: Tooth movement induced by interactive traction during orthodontic treatment causes regular spontaneous pain, however, the central nervous system conduction pathway and the basic mechanisms of pain are not clear.

OBJECTIVE: To establish rat models of experimental tooth movement and observe the behavioral variation of rat chewing-like jaw movements in unit time after tooth movement.

METHODS: Rats were randomly divided into blank, negative control and model groups. According to modified Colin. K. method, rat models of experimental tooth movement were established in the model group through interactive traction of the rat maxillary anterior and posterior teeth by orthodontic nickel-titanium wires. Rats in the blank group were not subjected to interactive traction treatment. Rats in the negative control group were not imposed corrective force. The behavioral variation of chewing-like jaw movements of rats was detected respectively at 4, 12 hours and at 1, 3, 5, and 7 days after tooth movement. At 1 day after tooth movement, relative variation of chewing-like jaw movements of rats was observed after imposing orthodontic force of 30, 60 and 90 g on movable tooth.

RESULTS AND CONCLUSION: Beginning from 4 hours after tooth movement, the total time of chewing-like jaw movements began to increase, and the time of chewing-like jaw movements was significantly increased at 12

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hours after tooth movement, reached the peak at 1 day after tooth movement, and then was slowly declined until 7 days in the model group compared with that in the negative control and blank groups. At 1 day after tooth movement, there was significant difference in the time taken for chewing-like jaw movements in the model group among orthodontic force of 30, 60 and 90 g ($P < 0.05$). These results confirm that the time variation of chewing-like jaw movements after tooth movement is consistent with the rule of pain induced by tooth movement during clinical orthodontic treatment, which can be used as one of the related behavioral responses of oral and maxillofacial pain after tooth movement in rats.

Subject headings: Tissue Engineering; Tooth; Pain; Models, Animal
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0 引言 Introduction

国际疼痛研究会分类学分会将疼痛定义为：一种不愉快的感觉及情绪体验，与实际发生和可能发生的组织损害有关或被描述为这种损害[1]。正畸疼痛严重影响患者对正畸治疗的接纳及配合程度，与正畸疗效密切相关圈临床正畸过程疼引起的疼痛不适疼痛发生率达91%[2]，正畸加力后持续3–5 d后逐渐缓解[3-5]。

既往研究表明，牙齿移动所致炎性疼痛与P物质，降钙素基因相关肽、白细胞介素1、前列腺素等炎性因子和神经递质等密切相关[6-11]。

正畸牙的移动过程是牙周组织在矫治力的间接作用下发生的一种炎症反应，在牙周的改建过程中，牙周膜内神经末梢也受到伤害性的机械刺激，牙周膜内的肥大细胞合成并释放了与炎症有关的化学递质和酶，如组胺、乙酰胆碱、缓激肽等，它们相互作用引起局部血管扩张，毛细血管渗透压增高，使牙周膜内感受器的敏感性升高，进而导致疼痛的阈值降低，牙周感受器对刺激更加敏感，此现象称为“痛觉过敏”[12-14]。

牙周释放的疼痛递质兴奋伤害感受器，经由牙周Aδ和C神经纤维传导至三叉神经节胞体，再投射至三叉神经脊束核尾侧亚核，神经元换元后交叉到对侧，上行传递至中脑、丘脑投射到大脑皮质的特定区域，最终形成痛觉[15-18]。但是疼痛发生的机制仍然不是很清楚。

动物实验文献追溯发现，啮齿类动物大鼠口颌面炎性、神经性疼痛相关的的行为学包括面部梳理(包括摇头，舔舐刺激部位，梳理毛发，擦拭面颊、嘴，耳朵区域)，空口咀嚼，眼睛凝视，眉弓收缩等表现[9, 19]，在甲醛等诱发的大鼠口颌面部疼痛的外周炎症实验模型中，空口咀嚼时间变化与口面部疼痛呈显著相关改变[19-23]。但是在研究牙齿移动疼痛发生过程中，将空口咀嚼时间纳入与炎性疼痛相关联的变化规律指标，以往中、外文献中未有提及。

实验模拟临床正畸治疗牙齿移动过程，建立大鼠前、后牙镍钛弹簧丝交互牵引牙移动模型，观察大鼠牙齿移动后不同时间点空口咀嚼时间变化规律，对比与临床正畸牙移动后导致的口颌面部疼痛规律，验证空口咀嚼这一特有行为学特征是研究牙齿移动后疼痛规律的有效的行为学方法之一，力求依据上述动物实验模型的顺利建立，完成牙齿移动后疼痛体征的外周、中枢神经通路的研究，初步探索、明确正畸牙移动疼痛的基础原因、特点及其可能的外周神经机制，寻找可能存在的靶点位置位于干预处理，应用于目前临床常用的缓解正畸疼痛方案，为制定临床治疗中切实可行的个体化方案提供参考。

1 材料和方法 Materials and methods

1.1 *造模动物及材料* 选用9周龄雄性SD大鼠36只，体质量200–250 g，由解放军总医院动物实验中心提供，动物合格证号：20140104836，安静环境中饲养72 h后进行实验。

镍钛拉簧购自北京有研亿金公司，直径0.18 mm；机械正畸测力计购自杭州新亚口腔器械公司；水合氯醛购自天津市红岩试剂厂；行为学摄像及分析系统购自上海移数公司。

1.2 *造模方法* 实验于2012年7月至2014年1月在解放军总医院动物实验中心和临床、实验研究中心完成。

分组：36只SD大鼠随机分为空白组(Naïve，*n*=6)，阴性对照组(Sham，*n*=6)，模型组(牙移动正畸矫治力60 g组，*n*=6)，在4 h，12 h，1 d，3 d，5 d，7 d等6个时间点分别对各模型组进行单位时间空口咀嚼时间和传统梳面行为学观测计数。为了进一步研究实验动物不同矫治力值单位时间空口咀嚼时间是否有改变，根据临床正畸牙移动后1 d时疼痛峰值，实验设计在大鼠牙齿移动后1 d时间点，观察分别加力后30，60，90 g此3组大鼠相同时间点，不同力值组单位时间空口咀嚼时间的变化。

构建正畸牙移动大鼠模型：采用改进Colin等使用的正畸牙移动实验模型方法[24]，设计实验所用正畸牙移动模型。盐酸水合氯醛腹腔注射麻醉大鼠后(0.002 mL/kg)，在右侧上颌前、后区域分别安放加力固位装置：上颌两中切牙邻龈缘处环形磨切约0.2 mm深的釉质浅沟，沟槽内放置不锈钢结扎丝(直径为0.2 mm)，环扎两切牙为一整体，将相同直径不锈钢结扎丝穿过大鼠右侧上颌第一磨牙与第二磨牙邻隙后，将镍钛螺旋拉簧(北京有研亿金公司，直径0.18 mm)

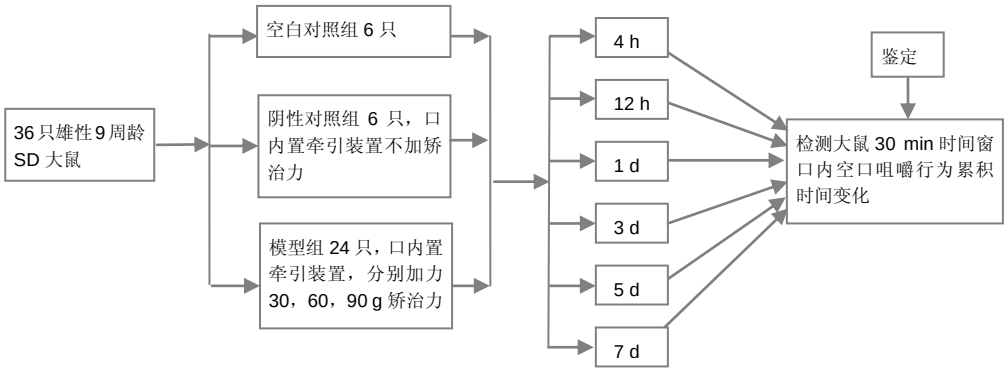

图 3　造模流程图

Figure 3　Flowchart of establishing rat models of experimental tooth movement

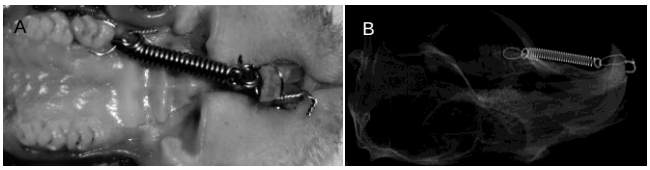

图 1　大鼠牙齿移动模型(第一磨牙近中移动 1.1 mm)

Figure 1　Rat models of tooth movement (mesial movement 1.1 mm of the first molar)

图注：图中 A 为口内观；B 为侧向 X 射线影像。

图 2　观察大鼠空口咀嚼时间行为学改变所用设备

Figure 2　Facilities used for observing behavioral changes of chewing-like jaw movements of rats

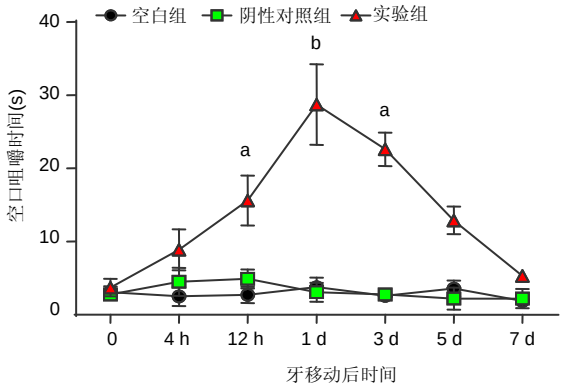

图 4　相同正畸矫治力(60 g)作用下，大鼠牙齿移动后不同时间点组间空口咀嚼时间变化

Figure 4　Time variation of chewing-like jaw movements between groups after tooth movement of rats under the same orthodontic force (60 g)

图注：与阴性对照组相比，$^{b}P < 0.01$；$^{a}P < 0.05$。

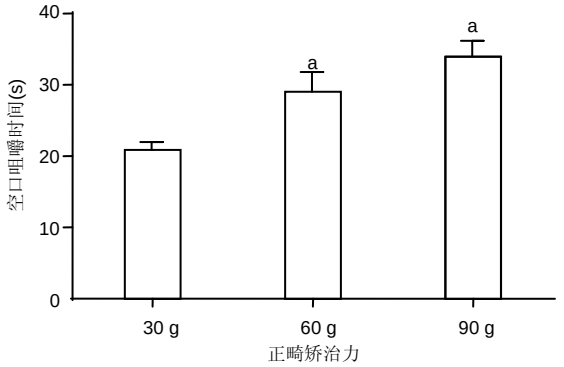

图 5　不同正畸矫治力值(30，60，90 g)，牙移动后 1 d 各组空口咀嚼时间变化

Figure 5　Time variation of empty chewing in each group at 1 day after tooth movement under different orthodontic force value (30, 60, 90 g)

图注：与 30 g 矫治力组相比较，$^{a}P < 0.05$。

置于右侧上颌第一磨牙与同侧切牙之间，前、后与相邻切，磨牙上钢丝结扎相连，使用测力计在NiTi螺旋拉簧受力后产生60 g交互牵引力(测力计杭州新亚口腔器械公司)，使磨牙产生近中倾斜移动的趋势(**图1**)，阴性对照组大鼠实施与模型组相同的实验过程但牵引力值为0 g，术后软食饲养动物。每日定时检查加力装置有无脱落，7 d后加力装置无脱落，大鼠解剖后第一磨牙移动大于0.5 mm为建模成功的标准。

1.3　造模成功的检测标准　实验动物疼痛行为观察：行为学观察开始前1 h，将大鼠放置在行为学实验室(恒温18–22 ℃、恒湿35%–45%、噪声小于45 dB)，待其熟悉环境后，分别将每只大鼠置于35 cm×35 cm×50 cm 透明玻璃观察箱内(底部放置数码摄像镜头SONY 50 mm定焦镜头)，静止15 min后开始录像，持续10 min，间隔20 min后，再次录像10 min，共3次，每只大鼠录像记录30 min，取其观察时

间内大鼠空口咀嚼时间总和平均值[19]。观察空白组、阴性对照组、模型组大鼠不同时间点(正畸牙移动后4，12 h及1，3，5，7 d)空口咀嚼时间总和的变化。

行为学观察时间段设置为上午9点到晚上6点之间，由1名不参与实验设计的行为学实验室工作人员完成实验录像及单位时间空口咀嚼时间计时整理。记录者依据自动录像装置获取的视屏资料，观察每只大鼠30 min时间窗口内空口咀嚼动作发生区间，同时应用手动计时器记录大鼠空口咀嚼累积时间(s)长短，见**图2**。

1.4 主要观察指标 ①一般情况观察，严格观察SD大鼠造模前、后时间点一般情况。②观察大鼠顺利造模完成，大鼠完成口内交互牵引牙齿移动装置后4，12 h及1，3，5，7 d观测口内镍钛弹簧加力装置有无脱落、大鼠第一磨牙近中位移大小，判断大鼠建模是否成功。③大鼠牙齿移动后炎性痛相关单位时间空口咀嚼累积时间行为学观察：大鼠完成口内交互牵引牙齿移动装置后4，12 h及1，3，5，7 d，将观察大鼠置于数码影像录制透明玻璃观察箱内，每只大鼠录像记录30 min。专有实验室工作人员完成实验录像及实验动物单位时间空口咀嚼时间计时整理。

1.5 统计学分析 数据以$\bar{x}\pm s$表示，采用SPSS 17.0软件(SPSS，Chicago，IL，USA)进行数据分析，组间数据差异的比较采用单因素方差分析和SNK法，检验水准α=0.05。

2 结果 Results

2.1 实验动物数量分析 纳入实验动物SD大鼠36只，进入结果分析36只，无死亡和感染，无脱失值，最终计入结果分析36只。

造模流程图见**图3**。

2.2 各组大鼠空口咀嚼时间变化 与阴性对照组，空白组相比较，模型组大鼠牙移动后4 h单位时间空口咀嚼时间总和开始增加，牙移动后12 h空口咀嚼时间明显增加(P < 0.05)，1 d达到峰值(P < 0.01)，随后缓慢下降至7 d，3组间空口咀嚼时间比较变化差异无显著性意义(P > 0.05)；阴性对照组和空白阴性对照组相比较，正畸牙移动后不同时间点大鼠空口咀嚼时间没有明显变化(P > 0.05)。见**图4**。与30 g矫治力组相比较，60，90 g矫治力组牙移动后1 d空口咀嚼时间均增加(P < 0.05)，见**图5**。

3 讨论 Discussion

如何缓解正畸过程疼痛是患者主要诉求之一，动物实验表明，大鼠牙移动后，牙周炎症因子，免疫因子及神经递质等均会有变化，痛觉信息经外周传导通路传递至中枢神经疼痛相关区域，使大鼠感知到自发疼痛[25-30]。大鼠空口咀嚼属于下意识自发行为，有时单独发生，通常会在大鼠有序梳理口、颌、面、部以及躯体、四肢皮毛过程中出现下意识空口咀嚼行为，单位时间内空口咀嚼时间相对恒定。文献证实，大鼠空口咀嚼时间在口颌面疼痛其他部位动物实验模型中会有明显改变[19, 31]。

实验结果首次证实：正畸牙移动模型组大鼠的空口咀嚼时间和阴性对照组比较显著增加，并且随时间变化有规律波动：大鼠的空口咀嚼时间在牙移动后4 h增加，约1 d达到峰值，随后会缓慢下降。这种行为学的变化规律和临床正畸首次使用弓丝进行牙移动患者出现的疼痛的变化规律相一致[2, 32-37]。实验结果表明：牙齿移动后不同时间点单位时间内空口咀嚼时间变化相对稳定、有规律，适合应用于探索实验性正畸牙移动疼痛相关实验检测行为学指标之一。

实验发现，随着正畸矫治力的增加，大鼠和疼痛相关的单位时间空口咀嚼时间也随之增加，这一发现与大鼠颌面部注射芥末油刺激形成外周炎症模型中，大鼠空口咀嚼时间改变与芥末油浓度改变呈正相关性变化一致[38]。另有实验使用甲醛局部刺激大鼠为疼痛模型，证实大鼠空口咀嚼时间的变化与使用不同剂量吗啡拮抗剂纳络酮干预疼痛明显相关[39-41]。上述大鼠牙移动后空口咀嚼时间变化随实验条件改变而相应改变的行为学特征支持将单位时间空口咀嚼时间变化规律作为研究牙移动后疼痛规律的行为学评估方法之一。

实验还观察到：大鼠牙移动不同时间点大鼠单位时间内直接擦拭嘴行为改变和大鼠空口咀嚼时间的变化趋势相一致[42-53]，即：牙移动后4 h大鼠单位时间直接擦拭嘴时间开始增加，约1 d达到峰值，牙移动后7 d组和阴性对照组相比较无明显差异。提示实验在进一步研究大鼠牙移动疼痛规律的实验中，能够结合观察两种或以上相关联的行为学变化，防止分析数据时丢失和疼痛相关信息，能得到更客观、准确的结果。

上述研究发现表明，单位时间空口咀嚼时间变化作为大鼠牙齿移动后出现口颌面部炎性疼痛行为学反应之一，是一个可重复、可依赖的检测方法，能够应用到啮齿类动物牙移动疼痛基础研究中，揭示正畸牙移动后疼痛发生的规律。

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作者贡献：第一作者和通讯作者构思并设计实验，并与第二，三作者共同分析文献资料。第一作者撰写文章。通讯作者校审。第一作者和通讯作者对实验负责。

利益冲突：所有作者共同认可文章无相关利益冲突。

伦理问题：实验过程中对动物的处置应符合2009年《Ethical issues in animal experimentation》相关动物伦理学标准的条例。

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学术术语：正畸牙移动后疼痛的机制？临床正畸过程口颌面区域痛疼引起的不适是正畸医生最常见问题之一，疼痛在正畸弓丝初次加力后随即出现，疼痛加力后持续 3–5 d 后逐渐缓解，正畸牙移动后疼痛发生率达 91%。既往研究表明，牙齿移动是由正畸矫治力累及牙周组织所致炎性疼痛且与一些炎性因子，神经递质等密切相关，但是牙移动所致疼痛发生机制并不清楚。动物模型是进行临床研究的最有效手段，在动物模型上模拟临床研究，并对所获得的数据进行分析，目前国内、外学者对正畸牙移动研究主要通过建立正畸牙移动动物模型进行，结合三叉神经脊束核，口颌面部伤害性刺激向中枢传导的重要门户，三叉神经脊束核尾侧亚核是口颌面部参与伤害性刺激传导的重要部位，进一步研究疼痛相关中枢神经通路研究，对于指导临床治疗具有现实意义，有助于阐明正畸疼痛的发病机制。

作者声明：文章第一作者和通讯作者对研究和撰写的论文中出现的不端行为承担责任。论文中涉及的原始图片、数据(包括计算机数据库)记录及样本已按照有关规定保存、分享和销毁，可接受核查。

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