



基于慢性炎性疼痛模型的艾灸抗炎镇痛介入时机研究*

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【摘要】目的 基于完全弗氏佐剂(complete Freund's adjuvant, CFA)诱导的慢性炎性疼痛模型,对比分析不同艾灸介入时间的抗炎镇痛效应差异,探寻艾灸抗炎镇痛的适宜介入时机,为艾灸抗炎镇痛的基础研究探寻规范的干预方案。**方法** 实验分为三部分,分别在造模后第4、7、10天开展艾灸介入时间的研究。每部分研究将雄性C57BL/6小鼠随机分为空白组、模型组和艾灸介入组,每组各8只。通过小鼠右侧足底注射20 μL完全弗氏佐剂建立慢性炎性疼痛模型。分别于造模后第4、7、10天给予“足三里”穴艾灸干预30 min,连续干预7天。于造模前和造模后以及艾灸治疗第1、4、7天检测热辐射刺激缩爪潜伏期评价痛阈,检测足容积评价足趾肿胀度。**结果** 与空白组比,模型组痛阈均降低($P < 0.0001$),足容积均增高($P < 0.0001$)。与模型组比,造模后第4、7、10天艾灸介入组痛阈升高($P < 0.05$, $P < 0.0001$);第4天艾灸介入组足容积反而升高($P < 0.0001$),第7、10天艾灸介入组足容积降低($P < 0.0001$)。第4、7、10天各艾灸介入组组间比较,第7天艾灸介入组痛阈升高显著($P < 0.05$, $P < 0.0001$),第7、10天艾灸介入组足容积降低显著($P < 0.0001$)。**结论** 综合艾灸镇痛和抗炎两方面效应来看,造模后第7天可能是艾灸发挥抗炎镇痛效应的适宜介入时机。

【关键词】 艾灸 介入时机 慢性炎性疼痛

Optimal Timing of Moxibustion Intervention for Anti-inflammatory and Analgesic Effects Based on a Chronic Inflammatory Pain Model ZHOU Ruizhu^{1,2,3}, HE Liuxuan^{1,2,3}, Hou Shuai^{1,2,3}, YANG Sha^{1,2,3}, YIN Haiyan^{1,2,3}, YU Shuguang^{1,2,3,Δ}. 1. Acupuncture and Tuina School, Chengdu University of Traditional Chinese Medicine, Chengdu 610075, China; 2. Key Laboratory of Acupuncture for Senile Disease (Chengdu University of TCM), Ministry of Education, Chengdu 610075, China; 3. Acupuncture and Chronobiology Key Laboratory of Sichuan Province, Chengdu 610075, China

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【Abstract】Objective Based on a complete Freund's adjuvant (CFA)-induced chronic inflammatory pain model, we compared and analyzed the differences in anti-inflammatory and analgesic effects of moxibustion intervention initiated at different timepoints, aiming to identify the optimal timing for moxibustion intervention. The goal is to establish standardized intervention protocols for basic research on the anti-inflammatory and analgesic effects of moxibustion. **Methods** Male C57BL/6 mice were randomly divided into 3 groups based on the moxibustion initiation timepoints of 4, 7, and 10 d after modeling. Then, the mice in each group were randomly assigned to 3 subgroups, including a control group, a model group, and a moxibustion group, with 8 mice in each subgroup. Chronic inflammatory pain was induced by injecting 20 μL of CFA into the sole of the right hind paw. Moxibustion applied at the "Zusanli" acupoint for 30 minutes started on the 4th, 7th, and 10th days after modeling, and the intervention continued for 7 days. The latency of paw withdrawal to thermal radiation was measured to evaluate the pain threshold before modeling, after modeling, and on the 1st, 4th, and 7th days of treatment. Foot volume was measured to assess toe swelling before modeling, after modeling, and on the 1st and 7th days of treatment. **Results** Compared with the control group, the model group exhibited a reduced pain threshold ($P < 0.0001$) and increased paw volume ($P < 0.0001$). Compared with the model group, the subgroups receiving moxibustion intervention initiated on the 4th, 7th, and 10th days post-modeling exhibited an increased pain threshold ($P < 0.05$, $P < 0.0001$). However, the paw volume of the subgroups receiving moxibustion intervention initiated on the 4th day post-modeling increased ($P < 0.0001$), while those of the subgroups receiving moxibustion intervention initiated on the 7th and 10th days post-modeling decreased ($P < 0.0001$). Among the intervention subgroups receiving moxibustion initiated on days 4, 7, and 10, the day 7 intervention-initiating subgroup showed significant increase in pain threshold ($P < 0.05$, $P < 0.0001$), and the day 7 and day 10 intervention-initiating subgroups showed significantly reduced paw volume ($P < 0.0001$). **Conclusion** Considering both the analgesic and anti-inflammatory effects of moxibustion, day 7 post-modeling may be the optimal time for moxibustion to achieve effective anti-inflammatory and analgesic outcomes.

【Key words】 Moxibustion Intervention timing Chronic inflammatory pain

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近年来, 艾灸在慢性炎性痛治疗方面优势逐步凸显^[1]。随着临床艾灸抗炎镇痛有效证据的日益增多^[2-4], 深入开展艾灸抗炎镇痛的动物实验需求也日益增强, 以深入揭示其作用机理, 为艾灸抗炎镇痛的临床应用提供坚实的科学实验依据。本课题组在前期完全弗氏佐剂(complete Freund's adjuvant, CFA)诱导的慢性炎性痛艾灸干预小样本预实验中发现, 过早介入艾灸干预会引起小鼠足部肿胀加重, 而非减轻。这一现象提示艾灸介入时间可能是影响艾灸抗炎镇痛的重要因素。鉴于此, 笔者查阅了关于艾灸抗炎镇痛的文献, 发现关于艾灸抗炎镇痛的介入时间点存在较大差异, 其治疗效应也不尽相同^[5-8]。由此可见, 在艾灸抗炎镇痛的基础研究领域缺乏艾灸抗炎镇痛介入时间共识性、规范化的实验设计方案, 导致研究结果的可比性较低, 也在一定程度上限制了艾灸的推广应用和深入研究。鉴于此, 本研究基于针灸抗炎镇痛常用模型——CFA诱导的慢性炎性痛模型^[9], 通过对比分析不同艾灸介入时间的抗炎镇痛效应差异, 探寻艾灸抗炎镇痛的适宜介入时机, 为艾灸抗炎镇痛基础研究探寻规范性实验干预方案。

1 材料与方法

1.1 实验动物与分组

SPF级C57BL/6J小鼠72只, 雄性, 6~8周龄, 体质量(20±2)g, 由成都达硕公司提供[许可证号: SCXK(川)2022-0039], 饲养条件: 12 h明暗交替, 室温(23±2)℃, 湿

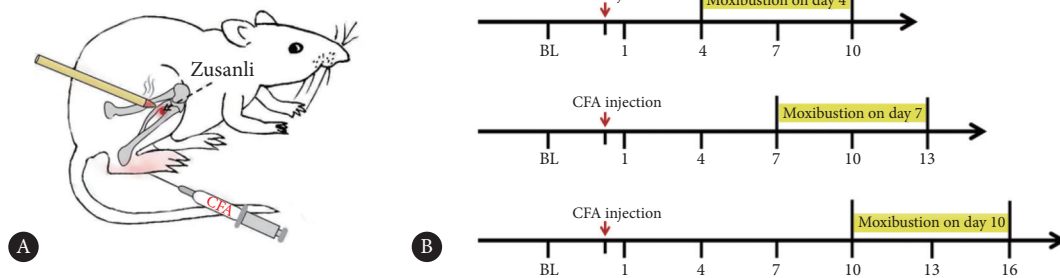


图 1 艾灸干预方法及实验流程图

Fig 1 Moxibustion intervention method (A) and flowchart of moxibustion intervention initiated at different points of time (B)

BL: baseline; CFA: complete Freund's adjuvant.

1.5 热痛阈检测

于造模前、造模后、治疗第1、4、7天检测热辐射刺激缩爪潜伏期(thermal withdrawal latency, TWL)评价痛阈。正式测量前, 将小鼠放入检测透明盒内适应30 min, 待其安静后, 将光源对准小鼠右侧足底后开启计时, 当小鼠出现明显的缩足反射时, 仪器终止计时, 该时间即为热痛阈值(s), 为避免长时程热辐射导致组织损伤, 热辐射时程控制在20 s之内, 刺激强度设置为20%(0.52 W); 测量

度50%左右, 自由摄食饮水。本实验分为三部分进行研究, 包括造模后第4、7、10天艾灸介入时间研究。正式实验之前小鼠适应性喂养7 d后, 每部分随机分为空白组(Control组)、模型组(CFA组)、艾灸介入组(CFA+Moxibustion组), 每组8只。本研究所有动物实验均按照美国国立卫生研究院(NIH)《实验动物护理和使用指南》进行, 并经成都中医药大学实验动物伦理委员会批准(审查号: 2025011)。

1.2 主要试剂及仪器

CFA(Sigma, 美国), 艾条(4 mm×12 mm, 南阳神农艾草), 热刺痛仪(PL-200, 成都泰盟), 动物足容积测量仪(PV-200, 成都泰盟)。

1.3 模型制备

于热痛阈值和足容积基线测试结束后对小鼠右后足皮下注射20 μL CFA制备慢性炎性疼痛模型, 空白组注射20 μL生理盐水。造模后小鼠右后足出现明显的红肿, 热痛阈值降低超过50%, 且足容积增加超过50%, 则造模成功。

1.4 艾灸干预

分别于造模后第4、7、10天开始艾灸干预。选取小鼠右侧“足三里”穴(膝关节后下方, 在腓骨小头下约3 mm, 胫骨外侧约2 mm处的肌沟中)进行施灸, 点燃的艾条置于并保持在与施灸穴位水平距离1 cm处。艾灸干预每天1次, 每次30 min。连续治疗7 d。实验设计如图1。

3次, 每次间隔5 min, 取3次平均值。实验均在室温(23±2)℃条件下进行。

1.6 足趾肿胀度测量

于造模前、造模后、治疗第1、7天用足容积测量仪检测足容积(paw volume)评价足趾肿胀度。确保足部完全浸入水中, 水位与脚踝处于同一水平线上, 设备进行读数记录体积, 重复以上步骤3次, 取平均值, 每次结束进行校准。实验均在室温(23±2)℃条件下进行。

1.7 统计学方法

计量资料以均数±标准误表示, 采用 Graph Pad Prism 9.4 软件进行统计分析。热痛阈值、足趾肿胀度等多时点测量数据采用重复测量方差分析, 进一步组间比较采用SNK检验。选艾灸干预最后一天的热痛阈变化幅值(艾灸组痛阈-模型组痛阈)、足容积变化幅值(艾灸组足容积-模型组足容积)进行组间单因素方差分析, $P < 0.05$ 表示差异有统计学意义。

2 结果

2.1 不同介入时间艾灸干预后小鼠热痛阈值的比较

不同介入时间艾灸干预后小鼠热痛阈值的比较结果

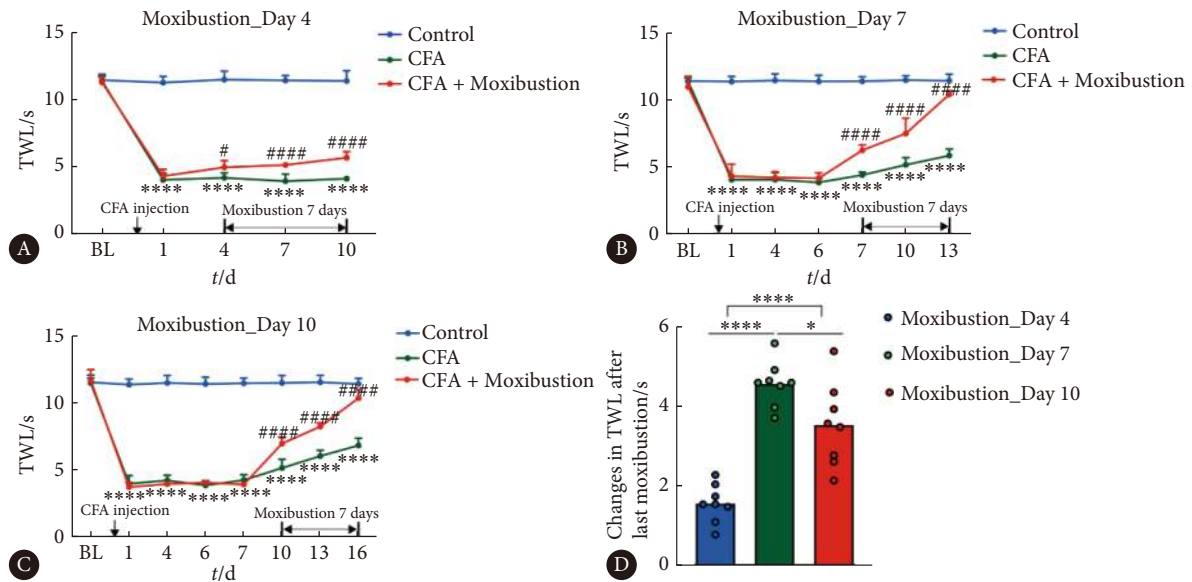


图 2 不同艾灸介入时间(造模后第4、7、10天)各组痛阈值比较

Fig 2 Comparison of TWL among groups receiving moxibustion intervention initiated at different timepoints (4, 7, and 10 d after modelling)

BL: baseline; CFA: complete Freund's adjuvant; TWL: thermal withdrawal latency. A-C, Changes in TWL in each group ($n = 8$), **** $P < 0.0001$, vs. control; * $P < 0.05$, **** $P < 0.0001$, vs. CFA; D, changes in TWL after last moxibustion in each group ($n = 8$), * $P < 0.05$, **** $P < 0.0001$.

2.2 不同介入时间艾灸干预后小鼠足容积的比较

不同介入时间艾灸干预后小鼠足容积的比较结果见图3。造模后, 各模型组小鼠在各时间点足容积均较空白组升高($P < 0.0001$)。艾灸首次干预当天, 各艾灸介入组足容积变化均不明显($P > 0.05$)。艾灸干预第7天, 第7天和第10天艾灸介入组, 其足容积较模型组均降低($P < 0.0001$); 而第4天艾灸介入组, 其足容积在艾灸第7天未见下降, 反而升高($P < 0.0001$)。

造模后第1天模型组足容积即达到峰值, 并维持10天左右的肿胀平台期, 约第10天足容积开始出现下降趋势(图3A~3C)。鉴于上述结果, 本研究对造模后第4天、第7天、第10天开始介入艾灸的小鼠, 于最后一次干预(即艾灸第7天)的足容积变化幅值(艾灸介入组足容积-模型

见图2)。造模后, 各模型组小鼠在各时间点热辐射痛阈值均较空白组降低($P < 0.0001$); 艾灸首次干预当天, 各艾灸介入组热痛阈值均提高($P < 0.05$, $P < 0.0001$); 艾灸干预第4天和第7天, 各艾灸介入组热痛阈值较模型组均提高($P < 0.0001$)。

约造模后第10天, 各模型组痛阈值逐渐抬高, 但艾灸干预前相比其抬高的幅值远低于艾灸干预组(图2A~2C)。本研究对造模后第4天、第7天、第10天开始介入艾灸的小鼠, 于最后一次干预(即艾灸第7天)的热痛阈变化幅值(艾灸介入组痛阈-模型组痛阈)对比分析, 结果显示第7天介入艾灸干预热痛阈值变化高于第4、10天($P < 0.05$, $P < 0.0001$), 见图2D。

组足容积)对比分析, 结果显示第7天和第10天艾灸介入组足容积变化幅值均低于第4天($P < 0.0001$), 且第7天与第10天艾灸介入组足容积变化幅值相当($P > 0.05$), 见图3D。

3 讨论

灸法是针灸学科的重要组成部分, 越来越多的研究证实艾灸抗炎镇痛、调节免疫是艾灸临床的优势适应证^[1, 10-11]。临床上, 艾灸常被用来治疗类风湿关节炎^[12-13]、膝关节关节炎^[14-15]、溃疡性结肠炎^[4, 16]等疾病。随着针灸作用机理研究的不断深入, 艾灸作用机理的基础研究也越来越多。纵观针灸机理文献, 不难发现, CFA模型是艾灸作用机理研究中较为常用的模型, 这是因为CFA模型是

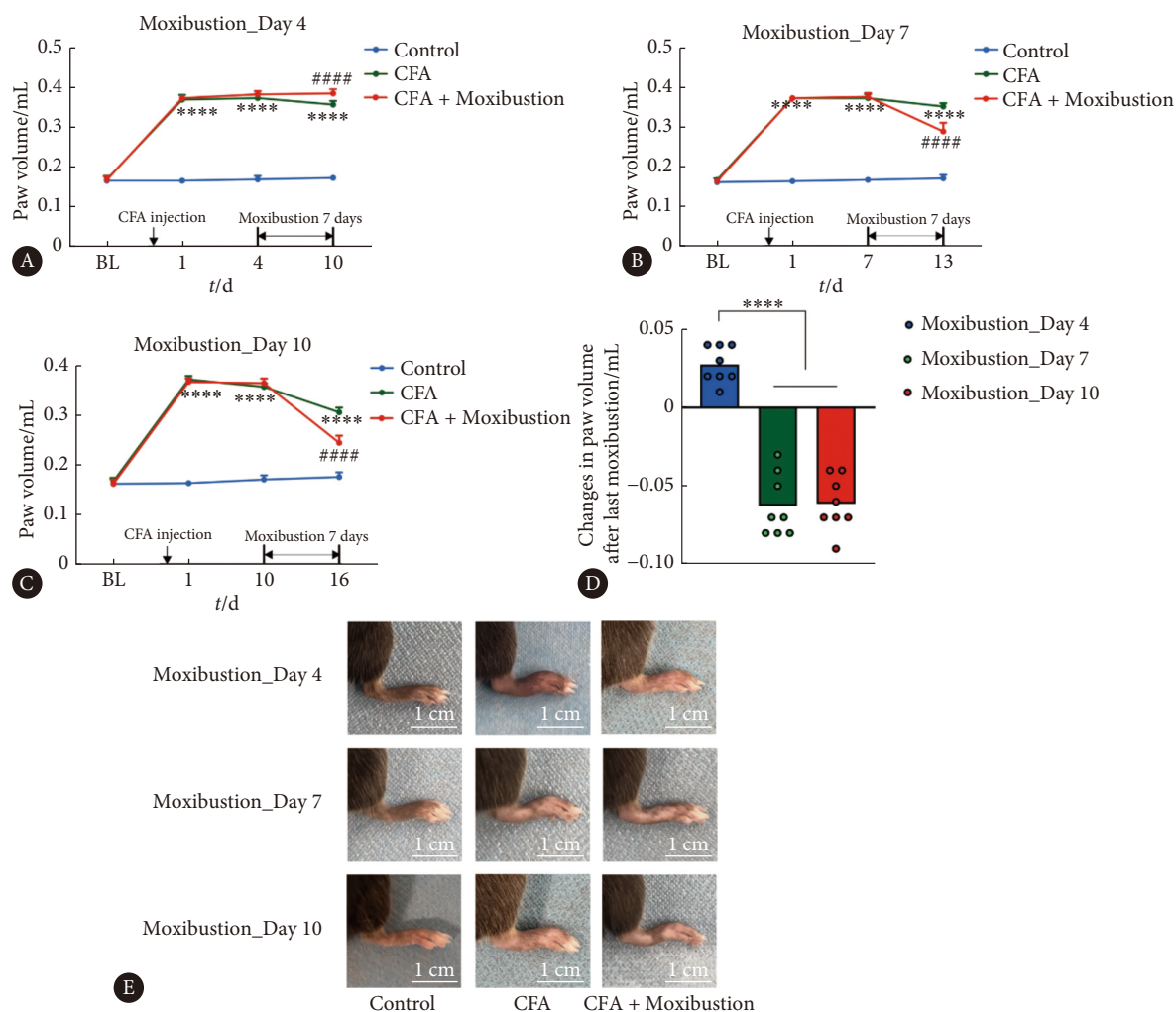


图 3 不同艾灸介入时间(造模后第4、7、10天)各组足容积比较

Fig 3 Comparison of paw volume in groups receiving moxibustion intervention initiated at different timepoints (4, 7, and 10 d after modelling)

BL: baseline; CFA: complete Freund's adjuvant. A-C, Changes in paw volume in each group ($n = 8$), **** $P < 0.0001$, vs. control; **** $P < 0.0001$, vs. CFA; D, changes in paw volume after last moxibustion in each group ($n = 8$), **** $P < 0.0001$; E, pictures of the right foot of mice after last moxibustion in each group ($n = 8$).

动物实验中常用的模拟炎症、疼痛、免疫紊乱相关症状的模型^[17-19],而且CFA模型制备操作简单、症状稳定。我们课题组也一直用CFA模型进行艾灸抗炎镇痛效应机理研究^[7,20-22]。

介入时机被认为是针灸疗效的关键影响因素之一^[23],而目前关于艾灸在慢性炎症疼痛治疗中的最佳介入时机尚未统一,研究涉及的介入时间多种多样,包括CFA造模后第2天^[5]、第3天^[6]、第4天^[7,16]、第8天^[8]等。课题组前期在小样本实验中也发现,艾灸并非干预越早抗炎镇痛效果越好,提示艾灸作用可能受干预时机影响。因此本研究将镇痛与抗炎效应结合在一起对比分析造模后第4、7、10天的艾灸干预效果,综合评估了不同介入时机对慢性炎症疼痛小鼠的镇痛和抗炎效应,以期探寻艾灸抗炎镇痛的适宜介入时机,为相关研究提供规范性参考。

研究结果显示,无论是造模后第4天、第7天、还是第

10天介入艾灸,均有较好的即刻镇痛效应,即干预当天即有效,且艾灸镇痛效应会随着艾灸次数的增加而逐渐累积增加,这与其他的研究结果一致^[5-8]。值得关注的是,约造模后第10天,模型组的痛阈会逐渐有小幅抬高,提示可能是模型组小鼠逐渐产生了疼痛耐受。因此,结合疼痛模型基线的变化来评估艾灸镇痛效应可能才是合理的策略。基于模型组和艾灸组痛阈变化幅值进一步分析发现,CFA造模后第7天艾灸介入镇痛效果显著优于第4天、第10天艾灸介入。在抗炎效应方面,结果显示造模后第7天和第10天艾灸介入足容积则显著降低,这与其它相关报道结果一致^[24],且第7天和第10天艾灸介入足容积的降低幅值相当。第4天介入艾灸,艾灸组足容积不降反升,提示艾灸抗炎效应不是越早越好,这可能是因为第4天尚属于急性炎症期,此刻介入艾灸可能会加重炎症。但第4天介入镇痛效应却显著,也提示艾灸抗炎、镇痛所

涉及的生物学基础可能不同^[25], 值得我们在艾灸抗炎镇痛机制研究中深入思考。

综上, 本研究结果表明对于CFA诱导慢性炎性疼痛模型, 造模后第7天介入艾灸可能是艾灸抗炎镇痛的适宜介入时期。该研究在一定程度上为艾灸抗炎镇痛机理研究提供了研究方案规范的参考, 同时也给临床艾灸抗炎镇痛的应用在介入时机方面提供一些思考。然而本研究亦存在不足之处, 首先仅基于CFA诱导的慢性炎性疼痛模型, 尚未验证其他慢性炎性疼痛模型或神经病理痛模型干预时机, 其次未进一步解析艾灸抗炎和镇痛机制可能涉及的不同分子通路。未来要结合多种疼痛模型病理特点及艾灸作用特点进一步明确干预时机, 此外还需通过分子机制研究深入探讨艾灸抗炎与镇痛生物学机制。

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Declaration of Conflicting Interests All authors declare no competing interests.

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