LIPUS 治疗慢性疼痛的研究进展

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摘要：慢性疼痛是指因组织损伤或者病理状况而产生的持久性疼痛感，其病理机理包含神经致敏，炎症持续以及组织修护受阻等多种因素的复杂交互影响。当下临床上常采用抗炎镇痛药物来医治慢性疼痛，阿片类药物和非甾体抗炎药就属于此类，不过这些药物常常会带来诸如胃肠道不适，睡眠障碍之类的严重影响健康的功能性副作用，从而制约了它们在临床上的全面推广，无创物理治疗手段在慢性疼痛治疗方面渐渐被人们所看重，光疗，声音疗法等就属于此类，超声疗法也是一种传统的无创物理刺激方法，在慢性疼痛治疗上慢慢表现出它的应用价值。低强度脉冲超声（Low-intensity pulsed ultrasound, LIPUS）以低强度传递，并以脉冲波形式输出，具有非热效应，仍然可以将声能传递给目标组织，给临床应用供应无创物理刺激，具有不会造成感染，不会损害组织，没有不良反应等优势，近些年，分子生物学，细胞力学以及医学成像技术不断发展，有关研究对于 LIPUS 镇痛机制的认知不再停留在宏观层面，而是逐步深入到细胞信号传导途径以及基因调控层次，这就为 LIPUS 在临床上的精确应用构筑了牢靠的理论根基，此综述尝试全面整理 LIPUS 治疗慢性疼痛涉及的机制及其临床应用的最新动态，进而为 LIPUS 的诊疗供应参照。

关键词：慢性疼痛；LIPUS；作用机制；临床应用

Abstract: Chronic pain refers to persistent pain caused by tissue damage or pathological conditions. Its pathological mechanism involves complex interactions of various factors such as nerve sensitization, persistent inflammation, and blocked tissue repair. Currently, anti-inflammatory and analgesic drugs are commonly used in clinical treatment of chronic pain. Opioid drugs and non-steroidal anti-inflammatory drugs fall into this category. However, these drugs often cause functional side effects such as gastrointestinal discomfort and sleep disorders that significantly affect health, thereby restricting their comprehensive promotion in clinical practice. Non-invasive physical therapy methods have gradually gained attention in the treatment of chronic pain. Phototherapy and sound therapy are among these. Ultrasound therapy is also a traditional non-invasive physical stimulation method, and it gradually demonstrates its application value in the treatment of chronic pain. Low-intensity pulsed ultrasound (LIPUS) transmits at a low intensity and outputs in the form of pulse waves. It has non-thermal effects and can still transfer acoustic energy to the target tissue, providing non-invasive physical stimulation for clinical application. It has advantages such as no infection, no tissue damage, and no adverse reactions. In recent years, advancements in molecular biology, cell mechanics, and medical imaging technologies have led to a shift in understanding of the pain-relieving mechanism of LIPUS from the macroscopic level to the cellular signal transduction pathways and gene regulation levels. This has laid a solid theoretical foundation for the precise application of LIPUS in clinical practice. This review attempts to comprehensively summarize the mechanisms involved in LIPUS treatment of chronic pain and the latest developments in its clinical application, thereby providing a reference for LIPUS diagnosis and treatment.

Keywords: chronic pain; LIPUS; mechanism of action;clinical application

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1 LIPUS 的技术特点与镇痛机制研究

1.1 LIPUS 的技术特点

LIPUS 属于利用脉冲形式来达成治疗目的的物理因子，当下常采用的脉冲频率有 3MHz 和 1.5MHz，脉冲重复频率为 1kHz，时间强度为 60mW/cm2 和 30mW/cm2，因为其强度较低（<3W/cm2），所以能突出减小由它引发的热效应并提升非热效应，而非热效应重点包含声流，传质加强以及空化现象[1]。当前临床上诊治疾病大多依靠它的非热效应，而且该效应受脉冲频率，占空比，治

疗时间等诸多参数的影响，这便为制订个性化治疗方案形成了根基。LIPUS 主要用于骨折之后，韧带，肌腱等软组织受损后的复健[2]，皮肤溃疡的愈合，瘢痕组织的软化[3]，疼痛等不良体感的改善，还能够加快血液循环，推动组织新陈代谢等。

1.2 LIPUS 多维镇痛机制解析

1.2.1 改善与调控局部微环境

LIPUS 改善局部微环境的关键机制源于 LIPUS 声波产生的稳定空化效应及声流现象[4]。相关研究显示，在糖尿病周围神经病变这种缺血性慢性疼痛模型当中，LIPUS 经由加强血管内皮细胞内皮型一氧化氮合酶(eNOS)活性来推动一氧化氮（NO）合成，进而激活 cGMP - PKG 信号通路并扩张微血管，使得作用部位血流量增长 35% - 50%，从而改善受损组织的缺氧状况，减轻由于缺血而引发的疼痛[5-7]。临床上已经证实 LIPUS 可以改善骨关节炎患者的关节微环境。相关研究显示，当 LIPUS 治疗骨关节炎患者时，患者关节滑液中的蛋白聚糖含量比治疗前增长了 25%，MMP-13 的水平大幅下降了 30%，而且，关节软骨的损伤情况得到了明显的改善，视觉模拟疼痛评分（VAS）也出现了大幅减小[8-10]。

在微环境调控当中，炎症协调属于关键的切入点。已有研究显示，LIPUS 会调节细胞离子通道的协调情况，比如 K+通道，Cl -通道，抑制 NLRP3 炎症小体被激活，减少炎症小体所促使的 IL-1β 释放，缩减氧化应激产物的汇集[11,12]，从而营造出低炎症，高供氧的微环境[13]。研究表明，巨噬细胞存在两种表型，M1 型大多推动炎症反应，M2 型更多地对抗炎症反应，LIPUS 能够抑制 M1 型向极化的方向发展，促使 M2 型发生转换[14]，减小 IL-1β，TNF-α 等促炎因子的分泌量，加大 TGF-β1 等抗炎因子的分泌量，使得局部炎症因子由促炎占优转为抗炎协调，重塑免疫稳定状态[15]。 LIPUS 可抑制 TLR4-MyD88 复合物及 NF-κB 核内易位的生成[16]，从而减轻成骨细胞因 LPS 引发的炎症反应。而且，LIPUS 能够抑制 TLR4-NF-κB 信号通路，以此来减小 LPS 影响 U937 巨噬细胞所产生的诸如 IL-6 和 IL-1β 等炎症因子的分泌量[17]。

LIPUS 具有稳定的空化效应及声流现象，这可经由调节细胞离子通道的均衡状况与基因表达模式来达成，从而提升组织的供氧量及其代谢效率，进而营造有益于改善疼痛的局部微环境。

1.2.2 促进组织修复

LIPUS 的机械效应会引发细胞振动，能加快细胞的新陈代谢，促使营养物质的运送并清除炎症产物，而且可以激活整合素受体以及一些参与组织修复的通路，比如 Rho，ERK 这些信号通路，从而推动胶原蛋白的合成，促使成纤维细胞增殖，加快受损组织的愈合进程，进而中断疼痛产生的生理机制[18,19]。有研究显示，LIPUS 能够促使骨髓间充质干细胞增殖分化，经由外泌体所引发的旁分泌作用来提升组织细胞的愈合能力[20-22]。LIPUS 还能借助提升血管内皮生长因子（VEGF）的表达水平，促使血管内皮细胞增殖，加强局部的血流灌注和营养供应，优化血管微循环状况[21,23]；LIPUS 还会抑制 MMP -13 降解酶的活性，有益于细胞外基质的重塑过程[18]。

1.2.3 调控神经信号

LIPUS 要达成对疼痛的调节功能，关键在于精准抑制外周神经的兴奋性，并对中枢疼痛网络的可塑性实施调节。

在周围神经系统当中，LIPUS 着重影响细胞的机械敏感性离子通道及关键痛觉相关离子通道。研究显示，LIPUS 可直接经由机械应力改变 Piezo1、K2P、TRPV1、Nav1.7 等通道，大幅缩减这些通道的过度表达情况，致使神经元动作电位发放频率改变，进而有效地提升压力疼痛阈值（PPT）[24-28]。以上提到的通道是痛觉信号产生与传导的起始阶段，LIPUS 通过影响此类通道抑制伤害性感受器异位放电与疼痛敏化，有益于针对痛觉信号生成的起始阶段实施干预[28,29]。先前研究表明，Piezo2 介导炎症和神经损伤引起的致敏机械性疼痛，靶向刺激 Piezo2 可能是治疗机械性异痛的有效策略[30]。而 Piezo2 作为机械敏感性离子通道，LIPUS 作用于 Piezo2 是否可有效减轻疼痛反应，有待进一步研究。

在中枢神经系统当中，LIPUS 大多经由激发内源性镇痛路径并逆转神经重塑的异常来达成镇痛效果。相关研究显示，LIPUS 可以促使中脑导水管四周灰质（PAG）以及延髓头端腹内侧区（RVM）分泌内啡肽和脑啡肽，加强脊髓背角 μ-阿片受体所引发的突触抑制现象，进而抑制痛觉信号向上传递[31,32]。近期的研究表明，当机体陷入慢性疼痛状况的时候，LIPUS 会提升前额叶皮层中 BDNF 的合成量，改善中枢神经元树突密度不正常的增多情况，促使中枢痛觉调控功能得到修复[33,34]。按照神经病理性疼痛模型来看，LIPUS 造成的中枢重塑效果

能够使得大鼠机械缩足阈值（MWT）提升超过60%，其镇痛作用还能维持四周[35]。这些研究成果给慢性疼痛的长远改善给予了机制方面的依据。

2 LIPUS在临床慢性疼痛疾病中的研究应用

2.1 神经病理性疼痛

神经病理性疼痛源于躯体感觉神经系统的损伤或者病变，其典型特征为烧灼痛，针刺痛以及电击痛，而且常常伴有痛觉过敏和感觉异常的情况，传统的治疗方法存在诸多不足，如疗效欠佳，副作用突出等[36]。近年来，LIPUS具备神经保护及神经修复能力[37]，慢慢发展成该类病症研究的焦点所在。

带状疱疹后神经痛（PHN）是临床上比较常见的顽固性神经病理性疼痛类型。针对PHN患者的观察性研究证实，LIPUS联合激素治疗的总有效率达88.33%，显著优于单纯激素治疗的70.00%,表明患者的疼痛与睡眠质量效果均得到有效改善，而且没有产生诸如皮肤刺激、激素相关不良反应的副作用[38]。在糖尿病周围神经病变疼痛（DPNP）治疗中，LIPUS也表现出较好的治疗效果。在一项纳入120例DPNP患者的临床研究发现，连续使用低频超声治疗治疗患者1个月、3个月及6个月的疼痛复发率分别为35.7%、10.0%和8.3%，且一年后患者的疼痛及相关临床症状都得到了明显改善[39]。研究表明，LIPUS与甲钴胺、神经生长因子等神经营养类药物联用可产生协同作用[40,41]，可以加快神经修复进程并延长镇痛效果的维持时间，这种长效镇痛机制或与调控神经微环境、抑制相关异常蛋白表达密切相关[42]。

LIPUS经由多通路，多靶点来发挥神经修护及镇痛功能，在PHN，DPNP等神经病理性疼痛病症中的效果较为明显，安全性也较高，与常规治疗药物配合时可加强疗效，给神经病理性疼痛的解决带来了新的临床思路，但是，对于其长期应用的稳定性以及合适人群的范围，还是得要开展更大规模的临床研究才能确定。

2.2 肌肉骨骼慢性疼痛

肌肉骨骼慢性疼痛属于全球范围的主要致残原因之列，其涵盖骨关节炎，慢性肌肉劳损以及肌腱韧带慢性损伤等诸多病症，核心病理变化包含组织退行性改变，慢性炎症过程以及纤维化现象[43]。近些年来，LIPUS具备减轻炎症反应并推动肌肉组织修复的能力，慢慢转变成该类疾病研究领域的关注焦点。

骨关节炎（OA）属于一种退行性疾病，其主要特点在于关节软骨出现退变情况，骨质发生增生现象，膝关节OA（KOA）较为常见。很多对比研究显示，LIPUS可以明显减轻KOA患者的疼痛症状，结合关节活动训练，肌力训练等常规物理疗法来治疗中度KOA患者的时候，效果比单纯采用常规物理疗法要好很多，患者的WOMAC评分和VAS评分都会大幅下降，而且膝关节的活动范围以及行走能力也得到了明显的改善，这个结论给KOA的非药物治疗带来新的参考[44,45]。也有研究显示，LIPUS用来医治因脊柱小关节OA而产生的慢性腰痛，可以明显改善腰部的活动状况[46,47]；这些治疗成果和LIPUS抑制MMP-13表达，促使Ⅱ型胶原合成，削减IL-1β，TNF-α的释放有着密切联系[48]，但是具体的机制还要做进一步的研究。

慢性肌肉劳损及肌筋膜疼痛综合征由肌肉长期处于紧绷状态并不断遭受损伤引发的慢性疼痛症状，颈肩腰背区域较为多发，突出表现局部肌肉紧绷，触发点按压时疼痛感强烈[49]。临床应用数据显示，接受LIPUS治疗的颈肩肌筋膜疼痛症患者，其VAS评分有所减小，触发点数目缩减，颈部活动范围亦得到优化，这种疗效与LIPUS所产生的机械震动有关，该震动可放松肌肉痉挛状况，改善局部血液循环及氧气供应状况，减轻炎性因子积聚程度[50,51]。部分临床操作显示，采用LIPUS配合传统手法实施康复训练之后，治疗效果更为理想。

肌腱，韧带的慢性损伤在运动人群和伏案工作者当中很常见，从病理角度看，肌腱或者韧带会出现纤维化现象，胶原纤维的排列变得混乱，还会存在慢性炎症浸润情况[52]。临床研究显示，经过LIPUS治疗之后，慢性跟腱炎患者的VAS评分明显降低，跟腱厚度大幅减小，患者走路，跳跃等功能也得以重建[53]。对于肩周炎患者来说，采用LIPUS结合关节松动术之后，肩部疼痛可以得到有效改善，关节活动幅度也能提升。这些治疗成果是因为LIPUS可促使腱细胞增殖，助力胶原纤维合成，加快受损组织的愈合进程，进而起到止痛并改善功能受限状况的作用[54]。

LIPUS经由调控炎性因子，加强细胞外基质合成，抑制纤维化等诸多途径，对肌肉骨骼慢性疼痛起到镇痛，抗炎及促修复的作用，与常规康复手段结合时会取得更为理想的疗效，给肌肉骨骼慢性疼痛的临床诊治带来安全有效的方向，但当下LIPUS在肌肉骨骼慢性疼痛方面的应用大多为小样本研究，大样本数据研究还需进一步

充实。

2.3 慢性盆腔疼痛综合征（CPPS）

CPPS 属于男性较为常见的泌尿系统疾病,其典型特征为持续三个月之久的盆腔疼痛，往往还伴有排尿困难，性功能异常等情况[55]，CPPS 的成因比较繁杂，当下临床上尚未找到理想的治疗方法，不过 LIPUS 这种非侵入性疗法带来了新希望。近年来的研究表明，LIPUS 能够调控 Th17/Treg 免疫细胞之间的协调关系，还能抑制 IL-1β/IL1R1/MyD88 炎症信号通路的活化，从而有效地减轻盆腔疼痛和前列腺发炎状况[56]。相关的临床研究也验证了 LIPUS 的效果，在一项专门针对 CPPS 患者的临床试验当中，经过 LIPUS 诊治之后，患者美国国立卫生研究院慢性前列腺炎症状指数（NIH-CPSI）里的疼痛分值，排尿分值以及生活质量分值都得到了明显的优化，而且没有产生诸如直肠受刺激，排尿不畅之类的副作用[57]。在临床应用中，LIPUS 同生物制剂、中药的联合治疗难治性 CPPS 患者，较单一疗法的疗效得以加强。随着对 LIPUS 在 CPPS 方面的治疗机制以及临床效果做更为细致的探究，LIPUS 大概会成为医治 CPPS 的一种重要方法。

3 总结与展望

LIPUS 属于无创性物理治疗方法，其发挥作用依靠改善局部微环境，调控神经信号，抗炎以及组织修复这些途径，在慢性疼痛治疗方面已显示出不错的临床应用潜力，不过当下 LIPUS 治疗仍然存在不少漏洞，比如治疗参数缺乏统一标准，相关机制的研究证据较少，这就在一定程度上限制了 LIPUS 在临床上的推广。近些年来，伴随 LIPUS 作用机制的研究逐步深入，临床治疗方面的证据慢慢增多，产品不断更新换代，LIPUS 有可能给慢性疼痛患者带来更为精确，安全又便于使用的物理疗法，其临床应用的未来值得憧憬。

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