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## 氯胺酮抗抑郁的临床研究

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**【摘要】** 氯胺酮作为一种新型的抗抑郁药得到越来越多的关注。本文对氯胺酮及其对映异构体(R-氯胺酮、S-氯胺酮)抗抑郁、抗自杀特性的临床研究进行探讨。

**【关键词】** 氯胺酮;抗抑郁;抗自杀

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### Clinical research progress on the antidepressant effects of ketamine

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**【Abstract】** Ketamine has gained increasing attention as a novel antidepressant. This article reviews the clinical studies on the antidepressant and anti-suicidal properties of ketamine and its enantiomers (R-ketamine, S-ketamine).

**【Keywords】** Ketamine; Antidepressant; Anti-suicidal

抑郁症是全球发病率和致残率最高的精神障碍<sup>[1]</sup>。20世纪50年代,抗高血压药物“利血平”被观察到会使人抑郁,同时消耗大脑中的单胺类神经递质(包括5-羟色胺和去甲肾上腺素)<sup>[2-4]</sup>,抑郁症的“单胺假说”一度盛行,单胺类抗抑郁药也成为治疗抑郁症的主要药物。然而单胺类和其他种类的抗抑郁药需要经过几周或数月的治疗才会显现出效果,而且约三分之一患有严重抑郁症的人对至少两种单胺类抗抑郁药无反应,为难治性抑郁症,伴有自杀意念和自杀行为的抑郁症患者短期内治疗反应也欠佳<sup>[5-7]</sup>。氯胺酮作为一种非竞争性的N-甲基-D-天冬氨酸(N-methyl-D-aspartic acid, NMDA)受体拮抗剂,被证实可以快速缓解抑郁症状、减轻自杀意念,也是近几十年来美国食品药品监督管理局(FDA)首次批准的新型抗抑郁药物<sup>[8]</sup>。本文就氯胺酮及其异构体抗抑郁、抗自杀的临床研究进行探讨。

### 1 氯胺酮抗抑郁效应

氯胺酮抗抑郁效应的发现最早可追溯到20世纪70年代,1975年Sofia等<sup>[9]</sup>的一项临床前研究表明,啮齿类动物使用氯胺酮后产生了与三环类抗抑郁药和单胺氧化酶抑制剂相似的作用。一项小型、双盲、安慰剂对照研究显示,氯胺酮具有抗抑郁作用,该研究纳入的9例抑郁症患者(包括8例重度抑郁症患者和1例双相抑郁患者)随机接受静脉注射亚麻醉剂量的氯胺酮(0.5 mg/kg)或生理盐水,以汉密尔顿抑郁量表(Hamilton Depression Scale, HAMD)

评分减分率不低于50%作为主要结局指标,共7例患者完成该研究,氯胺酮对其中4例患者产生了抗抑郁作用<sup>[10]</sup>。之后的多项临床研究也显示出氯胺酮对难治性抑郁症有效<sup>[11-13]</sup>。Zarate等<sup>[11]</sup>对难治性抑郁症患者给予氯胺酮单次静脉给药(0.5 mg/kg, 40 min),在给药后110 min内,患者抑郁症状明显改善,且抗抑郁效果平均持续7天。aan het Rot等<sup>[12]</sup>在此基础上进一步研究了氯胺酮重复静脉给药(每周3次、共6次)的抗抑郁效果和安全性,提示氯胺酮可用于急性期难治性抑郁症的治疗,且短期内未出现明显的认知功能损害。由于咪达唑仑和氯胺酮具有相似的药代动力学(起效快和消除半衰期短)和麻醉特性(如镇静和定向障碍),Murrough等<sup>[13]</sup>首次使用了活性安慰剂咪达唑仑为对照,结果显示接受氯胺酮治疗的患者应答率高于接受咪达唑仑治疗者(64% vs. 28%)。在延迟抑郁症复发方面,Daly等<sup>[14]</sup>的随机、双盲试验也显示,与安慰剂相比,氯胺酮可降低难治性抑郁症患者的复发风险。

氯胺酮同样可用于治疗双相抑郁。Diazgranados等<sup>[15]</sup>对18例难治性双相抑郁患者进行研究,与接受安慰剂治疗的患者相比,接受氯胺酮治疗的双相抑郁患者在40 min内抑郁症状改善,且效果持续到第3天。71%的患者对氯胺酮有反应,6%的患者在实验期间的某个时间点对安慰剂有反应。Zarate等<sup>[16]</sup>对15例难治性双相抑郁患者重复了该研究,79%的受试者在实验期间的某个时间点对氯胺酮有反应,没有受试者对安慰剂有反应。

Hu 等<sup>[17]</sup>的一项随机对照研究评估了单次氯胺酮静脉给药联合口服艾司西酞普兰治疗抑郁障碍的效果和安全性,结果显示在4周终点时氯胺酮联合艾司西酞普兰比单用艾司西酞普兰的临床治愈率更高(76.9% vs. 14.3%,  $P=0.001$ ),且达到临床治愈标准的时间更短,可弥补口服抗抑郁药起效延迟以及氯胺酮单次给药效果维持时间较短的缺陷。

## 2 氯胺酮抗自杀作用

氯胺酮可快速减少自杀意念,具有潜在的抗自杀作用。一项包括26例难治性抑郁症患者的开放性临床试验结果显示,氯胺酮不仅能快速改善抑郁症状,而且能在单次给药24 h内消除或缓解自杀意念,蒙哥马利-艾森伯格抑郁量表(Montgomery-Asberg Depression Rating Scale, MADRS)自杀条目评分降低2.08分,81%的患者在输注后24 h内自杀条目评分为0或1<sup>[18]</sup>。Diazgranados等<sup>[19]</sup>研究显示,氯胺酮输注后40 min内,难治性抑郁症患者自杀意念量表(Scale for Suicide Ideation, SSI)评分降低,且该指标在输注后4 h内显著降低。Larkin等<sup>[20]</sup>提供了氯胺酮用于伴自杀意念的急诊科抑郁症患者的可行性和有效性证据:14例伴有自杀意念的抑郁症患者在接受静脉推注氯胺酮(0.2 mg/kg)后1~2 min内自杀意念消退,给药后40 min抗抑郁作用起效,自杀评分的改善持续超过10天。

Zarate等<sup>[16]</sup>的一项双盲、随机、安慰剂对照研究显示,与安慰剂相比,接受氯胺酮治疗的双相抑郁患者在给药后40 min自杀意念减少,并持续3天。一项以咪达唑仑为对照的临床实验显示,氯胺酮对有强烈自杀意念的重度抑郁症患者效果更好,患者在24 h内自杀意念减少更多<sup>[21]</sup>。

国内外有研究分析了抑郁症患者氯胺酮治疗前后自杀意念和抑郁症状变化的关系,提出了氯胺酮可能具有独立于其抗抑郁作用的抗自杀作用<sup>[21~24]</sup>。研究表明,氯胺酮抗自杀作用的变异中大约只有三分之一可用其抗抑郁作用解释<sup>[24]</sup>,提示氯胺酮有在伴急性自杀风险的其他精神疾病中扩展其使用的可能。

## 3 异构体抗抑郁和抗自杀作用

氯胺酮是一种外消旋混合物,由两种异构体S-氯胺酮和R-氯胺酮组成。NMDA受体的拮抗作用在氯胺酮的抗抑郁机制中起重要作用,S-氯胺酮结合NMDAR效能是R-氯胺酮的3~4倍<sup>[25]</sup>。艾司氯胺酮是氯胺酮的S-异构体,在临床研究中被作为抗

抑郁药物使用。一项随机、双盲、安慰剂对照试验纳入30例难治性抑郁症患者,按1:1:1比例将患者随机分为三组,分别接受艾司氯胺酮0.2 mg/kg、艾司氯胺酮0.4 mg/kg和安慰剂40 min静脉输注,结果显示两种剂量的艾司氯胺酮治疗都在2 h内产生快速的抗抑郁作用,且两组在所有疗效指标上差异均无统计学意义,较低剂量的艾司氯胺酮在维持疗效的同时患者耐受性更好<sup>[26]</sup>。同样,艾司氯胺酮也具有潜在的抗自杀作用<sup>[27]</sup>。另一项随机、双盲、非劣效性研究评估了单次输注0.25 mg/kg艾司氯胺酮和0.5 mg/kg氯胺酮对难治性抑郁症的疗效和安全性,结果表明艾司氯胺酮的抗抑郁疗效不低于氯胺酮,且耐受性良好<sup>[28]</sup>。除了静脉给药,艾司氯胺酮经鼻给药也发挥着抗抑郁和抗自杀作用。一项二期、双盲、随机、安慰剂对照研究纳入67例难治性抑郁症患者,60例患者完成两个双盲期试验,患者按3:1:1:1比例分为安慰剂组、28 mg艾司氯胺酮组、56 mg艾司氯胺酮组和84 mg艾司氯胺酮组,每周两次经鼻给药。在第二期开放阶段,给药频率从每周两次减少到每周一次,再减少到每两周一次,结果显示三种剂量的艾司氯胺酮治疗组MADRS总评分(两个时期合计)的变化均优于安慰剂组,抑郁症状改善程度呈剂量-反应关系<sup>[29]</sup>。Canuso等<sup>[30]</sup>评估艾司氯胺酮经鼻给药对自杀意念的影响,研究显示,与安慰剂组相比,给药后4 h艾司氯胺酮组MADRS评分和自杀条目评分明显改善。鉴于其快速有效的初步临床获益,艾司氯胺酮鼻喷制剂已经获得FDA的两项认证,即用于难治性抑郁症患者和伴有严重自杀倾向的重度抑郁症患者<sup>[31]</sup>。但其疗效、长期使用的安全性和滥用倾向等仍需持续关注<sup>[32]</sup>。

关于R-氯胺酮的临床研究仍较少。2020年,一项开放性研究探索了R-氯胺酮对难治性抑郁症患者的抗抑郁疗效和安全性问题。在这项研究中,7例难治性抑郁症患者静脉注射0.5 mg/kg R-氯胺酮40 min内,抑郁症状改善,MADRS评分从输注前的30.7降至1天后的10.4,且患者解离症状等副反应发生较少<sup>[33]</sup>。虽然该研究样本量较小,且非对照研究,但也为R-氯胺酮抗抑郁的效果和安全性研究提供了一定的参考。

## 4 氯胺酮的不良反应及安全性

氯胺酮作为一种“分离性麻醉剂”,使用后会诱导出“与感官割离”的解离体验<sup>[34]</sup>,其致幻作用也使其成为舞厅聚会时常用的“助兴药品”,在全球范围

内被滥用<sup>[35-38]</sup>,并且氯胺酮可与阿片受体结合,预示其低剂量使用也可能具有成瘾性。已有研究表明,长期大量使用氯胺酮会出现膀胱炎、肾盂积水、腹痛、肝功能异常和认知功能损害等<sup>[39-43]</sup>。临床试验中单次氯胺酮使用者可出现工作记忆和情景记忆损害,频繁使用者短期记忆和长期记忆都会受到影响<sup>[42]</sup>。由于氯胺酮的作用时间通常不超过1周,临幊上用于维持治疗或者预防复发时则需要重复给药<sup>[44-45]</sup>。而关于重复使用氯胺酮的安全性数据非常有限,尤其对于青少年抑郁症患者认知功能的影响,仍需开展对照试验并进行长期随访,进一步明确氯胺酮使用剂量和使用频率<sup>[46]</sup>。但是,现有临幊研究观察到的氯胺酮不良反应较轻微,呈自限性的,不需要额外的治疗。氯胺酮长期给药疗效评估的相关报道尚缺乏,其远期安全性有待进一步评估。

## 5 小结与展望

氯胺酮自首次成功人工合成以来不到60年,作为抗抑郁药物使用的歷史更加短暂,虽然艾司氯胺酮鼻喷制剂已被FDA批准用于治疗抑郁症和改善自杀意念<sup>[32]</sup>,但上市后其安全性问题仍受到科学家的关注和质疑<sup>[47]</sup>。目前没有氯胺酮长期给药的疗效和远期安全性的评估,氯胺酮重复给药用于抑郁症的治疗和预防复发时仍应重视药物滥用的风险和认知功能损害等慢性不良反应<sup>[46]</sup>。从临幊前研究和现有临幊研究来看,R-氯胺酮的抗抑郁疗效和安全性似乎优于S-氯胺酮和R,S氯胺酮,比如,对啮齿类动物来说,R-氯胺酮的抗抑郁疗效更好且依赖行为发生更少<sup>[48-50]</sup>,并且小规模临幊研究显示,经其治疗后患者发生解离反应很少<sup>[33]</sup>。未来有必要进一步研究氯胺酮的抗抑郁机制,为未来抗抑郁药物研发寻找突破点,针对抑郁发生的内在原因选择更安全有效的抗抑郁药物。

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