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在线全文

艾司氯胺酮改善胸腔镜下肺癌根治术老年衰弱患者术后抑郁状态的随机双盲对照试验*

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【摘要】 目的 探究艾司氯胺酮对胸腔镜下肺癌根治术老年衰弱患者术后抑郁的影响。**方法** 选取择期行胸腔镜下肺癌根治术老年衰弱患者88例，以随机（随机化底表）双盲（方案实施者和患者）的方式分为艾司氯胺酮组（Esk组，n=44）和生理盐水组（NS组，n=44）。Esk组麻醉诱导时静脉推注0.25 mg/kg艾司氯胺酮，随后以每小时0.125 mg/kg的剂量持续输注至手术结束前20 min。NS组以同样方法输注等容量的生理盐水。主要结局为术后7 d和30 d的抑郁（HAMD-17量表）评分。次要结局为术后1、3、7和30 d的睡眠质量〔术后1、3和7 d用数字评定量表（numerical rating scale, NRS），术后30 d用匹兹堡睡眠质量指数（Pittsburgh Sleep Quality Index, PSQI）〕和认知功能（MMSE量表）评分。其他指标包括术后24 h（T1）、48 h（T2）和72 h（T3）血清脑源性神经营养因子（brain-derived neurotrophic factor, BDNF）、5-羟色胺（5-hydroxytryptamine, 5-HT）、S100β蛋白和神经元特异性烯醇化酶（neuron specific enolase, NSE）水平，以及围术期资料和术后安全性结果。**结果** Esk组和NS组各排除3例，最终每组各41例纳入统计分析。两组患者在年龄、性别、体质量指数、美国麻醉医师协会（ASA）分级、合并症、受教育程度及术前1 d量表（HAMD-17、PSQI和MMSE）评分等方面差异无统计学意义。主要结局：与NS组相比，Esk组患者术后7 d〔中位数（P_{25}, P_{75}）〕〔7（6, 8）vs. 7（6, 12），P=0.045〕和30 d〔6（6, 7）vs. 7（6, 9），P=0.020〕的HAMD-17评分降低。次要结局：与NS组相比，Esk组患者术后1、3和7 d的睡眠NRS评分降低（P<0.01），MMSE评分升高（P<0.05）。其他指标：与NS组比较，Esk组患者T1～T3时血清BDNF和5-HT浓度升高（P<0.05或<0.01）、S100β含量降低（P<0.01）；T1～T2时血清NSE水平降低（P<0.01）；术中丙泊酚、舒芬太尼、瑞芬太尼、七氟醚的消耗量减少（P<0.05或<0.01）；术后恶心/呕吐及痛觉过敏发生率降低（P<0.01）；术后呼吸机辅助时间、麻醉后监测治疗室（postanesthesia care unit, PACU）停留时间及术后住院天数缩短（P<0.01）。**结论** 艾司氯胺酮可改善胸腔镜下肺癌根治术老年衰弱患者术后抑郁状态、睡眠质量和认知功能。

【关键词】 艾司氯胺酮 老年衰弱患者 胸腔镜 肺癌根治术 术后抑郁状态

Esketamine Alleviates Postoperative Depressive Symptoms in Frail Elderly Patients Undergoing Thoracoscopic Radical Resection of Lung Cancer: A Randomized Double-Blind Controlled Trial

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[Abstract] Objective To investigate the effect of esketamine on postoperative depression in frail elderly patients undergoing thoracoscopic radical resection of lung cancer. **Methods** A total of 88 frail elderly patients undergoing elective thoracoscopic radical resection of lung cancer were assigned randomly (using a randomization table) and in a double-blind way (blinding applies to both researchers and patients) to an esketamine group (Esk group, n = 44) and a normal saline group (NS group, n = 44). In the Esk group, 0.25 mg/kg esketamine was injected intravenously during anesthesia induction, followed by continuous infusion of esketamine at 0.125 mg/kg per hour until 20 min before the end of surgery. In the NS group, equivalent volumes of normal saline were administered using the same method. The primary outcome was the score for the 17-item Hamilton Rating Scale for Depression (HAMD-17) on days 7 and 30 after surgery.

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The secondary outcomes included sleep quality and cognitive function. Sleep quality was assessed using the numerical rating scale (NRS) on days 1, 3, and 7 after surgery and the Pittsburgh Sleep Quality Index (PSQI) on day 30 after surgery. Cognitive function was assessed using the Mini-Mental State Examination (MMSE) on days 1, 3, 7, and 30 after surgery. The other indicators included the levels of serum brain-derived neurotrophic factor (BDNF), 5-hydroxytryptamine (5-HT), S100β protein, and neuron specific enolase (NSE) at 24 hours (T1), 48 hours (T2), and 72 hours (T3) after surgery, as well as perioperative data and postoperative safety outcomes. **Results** Three patients were excluded from the Esk group and the NS group, respectively, and eventually, 41 patients in each group were included in the statistical analysis. There were no statistically significant differences between the two groups in terms of age, sex, body mass index, American Society of Anesthesiologists (ASA) classification, comorbidities, educational attainment, and the scores for HAMD-17, PSQI, and MMSE 1 day before surgery ($P > 0.05$). Concerning the primary outcome, compared with those of the NS group, the HAMD-17 scores of patients in the Esk group were significantly lower at 7 days (median [P_{25}, P_{75}]) (7 [6, 8] vs. 7 [6, 12], $P = 0.045$) and 30 days (6 [6, 7] vs. 7 [6, 9], $P = 0.020$) after surgery. Concerning the secondary outcomes, compared with those of the NS group, the sleep NRS scores of patients in the Esk group were significantly lower at 1, 3, and 7 days after surgery ($P < 0.01$), and the MMSE scores were significantly higher ($P < 0.05$). Concerning the other indicators, compared with those of the NS group, the concentrations of serum BDNF and 5-HT in the Esk group were significantly higher ($P < 0.05$ or 0.01) at T1-T3, while the content of S100β was significantly lower ($P < 0.01$) at T1-T3; the levels of serum NSE were significantly lower at T1 and T2 ($P < 0.01$); the consumption of propofol, sufentanil, remifentanil, and sevoflurane during surgery in the Esk group was significantly reduced ($P < 0.05$ or 0.01); the incidence of postoperative nausea/vomiting and hyperalgesia was significantly lower ($P < 0.01$); the duration of postoperative mechanical ventilation, length-of-stay in postanesthesia care unit (PACU), and postoperative length-of-stay in the hospital were significantly shorter ($P < 0.01$). **Conclusion** Esketamine can improve the postoperative depressive state, sleep quality, and cognitive function in frail elderly patients undergoing thoracoscopic radical resection of lung cancer.

[Key words] Esketamine　Frail elderly patients　Thoracoscopy　Radical resection of lung cancer　Postoperative depressive state

肺癌是目前国内乃至世界上发病率和死亡率最高的恶性肿瘤之一[1-2]。根治性外科手术是早期非小细胞肺癌首选局部治疗方式[3]。随着加速康复外科(ERAS)理念的不断深入，胸腔镜下肺癌根治术已成为绝对的主流手术方式。然而，PARK等[4]进行的一项前瞻性临床研究结果显示，肺癌患者术后抑郁的发生率为19%。随着医疗水平的不断提高，接受手术的老年衰弱患者也在逐年增多[5]。我国住院老年患者中，衰弱发生率约为30%[6]。非心脏手术老年患者的衰弱发生率约为23%[7]。一项国外多中心研究显示，接受主动脉瓣膜置换术老年患者衰弱发生率高达68%[8]。衰弱老年患者生理储备下降、抗打击能力减退及应激后恢复能力下降是最具临床意义的老年综合征[9]。衰弱是导致老年人机能下降和致残的主要因素，与抑郁症状加剧及认知障碍程度加深密切相关[10-12]。而术后抑郁与认知功能障碍相互影响、相互制约[13]。术后睡眠障碍发生率可达44% ~ 71%[14-15]。术后睡眠质量与恢复质量直接决定患者术后转归[16]。术后抑郁是术后睡眠障碍的重要独立危险因素，睡眠质量直接影响患者的抑郁程度[17]。麻醉医生通过优化麻醉方案、完善术中监测等干预措施来降低患者术后疼痛等并发症的发生率，但在术后精神状态及睡眠质量的改善方面收效甚微。因此，降低患者术后抑郁、睡眠及认知功能障碍的发生率，提高患者术后恢复质量是临床上亟需解决的难题。

艾司氯胺酮，作为氯胺酮的右旋异构体，主要通过非竞争性地阻断N-甲基-D-天冬氨酸(NMDA)受体而起到较强的镇痛作用，还具有对呼吸和循环影响较小等特点，因此被广泛应用于临床[18-19]。近年来的临床研究中，艾司氯胺酮越来越多地被用于预防抑郁和自杀[20-21]。然而，艾司氯胺酮对老年衰弱患者术后抑郁的影响及其可能机制目前尚不明确。

本研究拟以胸腔镜下肺癌根治术老年衰弱患者为研究对象，应用艾司氯胺酮进行干预，观察其对术后抑郁、睡眠质量及认知功能的影响，以期为改善老年衰弱患者术后精神心理状态、提高术后恢复质量提供新的研究思路和预防措施。

1　资料与方法

1.1　研究对象

纳入标准：年龄65 ~ 80岁，性别不限，体质量指数(body mass index, BMI)18 ~ 30 kg/m^2，美国麻醉医师协会(ASA)分级为Ⅱ或Ⅲ级，且满足FRAIL衰弱评估量表中的3条及以上[22]；术前支气管镜或穿刺病理学检测结果确诊

为肺癌或临床高度怀疑肺癌者;符合《中华医学会肺癌临床诊疗指南(2023版)》中的外科治疗标准[3],且经过评估可以耐受全麻胸腔镜下肺癌根治术;征得患者及家属同意,并签署麻醉及项目知情同意书。排除标准:术前存在精神系统疾病或服用抗精神类药物;对艾司氯胺酮等麻醉药物过敏;存在神经阻滞禁忌;术前有严重心(NYHA Ⅳ级)、肝(Child-Pugh C级)、肾(透析)功能不全。剔除标准:手术方式改变(如肺叶楔形切除、开胸等)或计划外再次手术;术后病理结果为良性;术后拒绝电话随访;数据资料不全。

分组及盲法:Esk组麻醉诱导时静脉推注0.25 mg/kg艾司氯胺酮,随后以每小时0.125 mg/kg的剂量持续输注至手术结束前20 min。NS组以同样方法输注等容量的生理盐水。应用在线随机化工具(临床试验统计网)产生随机化底表,按照Esk组和NS组1∶1的比例进行区组随机,区组大小为4。将产生的随机数字底表密封于连续编号的随机信封,保管于试验协调员处。麻醉诱导前,试验协调员根据分组情况将配制好的药品交给麻醉医生,艾司氯胺酮和生理盐水均为无色透明液体且注射器的外观相同,故难以区分。试验协调员不参与数据的收集、录入及统计学分析。受试者、麻醉医生、外科医生、护理人员及术后随访者对分组情况均不知情。

样本量估算:应用PASS 15.0软件进行样本量估算。预实验结果显示,术后7 d Esk组和NS组患者的HAMD-17评分分别为7.0±3.6和9.1±2.9,设置双侧假设检验,Power为0.8,α为0.05,N1=N2。得出每组样本量为40,假设脱落率为10%,共招募88例符合纳入标准的患者,每组各44例。

纳入2023年8月–2024年6月在蚌埠医科大学第一附属医院胸外科行胸腔镜下肺癌根治术老年衰弱患者88例,随机分为Esk组和NS组,每组44例。本研究获蚌埠医学院伦理委员会批准(伦科批字[2023]第211号)。

1.2 麻醉方法

常规禁食禁饮。所有患者采用静脉-吸入复合全麻联合超声引导下竖脊肌平面阻滞。常规心电监护,桡动脉穿刺置管,监测有创动脉压。麻醉诱导:依次经外周静脉推注咪达唑仑0.05 ~ 0.1 mg/kg、依托咪酯0.2 ~ 0.3 mg/kg、舒芬太尼0.3 ~ 0.5 μg/kg、罗库溴铵1 ~ 1.5 mg/kg进行麻醉诱导。纤维支气管镜引导下支气管导管插管。超声引导下竖脊肌平面阻滞:患者取侧卧位。消毒铺巾,将无菌高频线性超声探头置于T5水平旁正中矢状位,旁开2 ~ 3 cm,找到T5横突。头侧进针(平面内),针尖触及横突,确认回抽无血后推注0.25%的罗哌卡因1 ~ 3 mL,若竖脊肌与横突明显分离(提示位置正确),继续推注剩余罗哌卡因(共20 mL)。麻醉维持:每小时持续静脉输注丙泊酚2.5 ~ 5 mg/kg、瑞芬太尼2 ~ 5 μg/kg和罗库溴铵1 ~ 1.5 mg/kg,间断静脉推注舒芬太尼(每次1 ~ 1.5 μg/kg)。术中维持呼气末二氧化碳分压($P_{ET}CO_2$)在35 ~ 45 mmHg(1 mmHg=0.133 kPa)之间、脑电双频指数(BIS)值40 ~ 60、平均动脉压变化波动不超过基础值的20%、心率60 ~ 80 min^{-1}。术毕静脉镇痛泵镇痛,配制方案:用生理盐水将舒芬太尼(0.5 ~ 1 μg/kg)、地佐辛(0.3 ~ 0.5 mg/kg)和托烷司琼(0.1 ~ 0.2 mg/kg)稀释至100 mL;参数设置:负荷剂量3 mL,持续输注速度2 mL/h。

1.3 观察指标

1.3.1 主要观察指标

术后7 d和30 d的抑郁(17-item Hamilton Rating Scale for Depression, HAMD-17量表)评分。HAMD-17量表,≥8分诊断为抑郁,得分越高说明抑郁程度越深。患者出院后主要通过电话及微信进行术后随访和量表评分。

1.3.2 次要观察指标

术后1 d、3 d、7 d和30 d的睡眠质量和认知功能(Mini-Mental State Examination, MMSE)评分。术后1 d、3 d和7 d睡眠质量用数字评定量表(numerical rating scale, NRS)法,术后30 d用匹兹堡睡眠质量指数(Pittsburgh Sleep Quality Index, PSQI)量表。PSQI量表(0 ~ 21分)和睡眠NRS评分(0 ~ 10分),得分越高说明睡眠质量越差。MMSE量表,总分30分,<27分诊断为认知功能障碍,得分越低说明认知功能障碍程度越深。

1.3.3 其他指标

术后24 h(T1)、48 h(T2)和72 h(T3)外周静脉血中脑源性神经营养因子(brain-derived neurotrophic factor, BDNF)、5-羟色胺(5-hydroxytryptamine, 5-HT)、S100β蛋白和神经元特异性烯醇化酶(neuron specific enolase, NSE)水平(ELISA法);术中麻醉药物消耗量、液体出入量、手术时长、术后呼吸机辅助时长、麻醉后监测治疗室(postanesthesia care unit, PACU)停留时长、术后住院天数等围术期资料;术后24 h和48 h静息和咳嗽时疼痛NRS评分、术后恶心/呕吐、皮肤瘙痒、头痛/头晕、幻觉/噩梦、躁动、苏醒延迟和痛觉过敏等安全性结果情况。

1.4 统计学方法

应用SPSS 25.0软件对数据进行分析处理。正态分布数据用$\bar{x}\pm s$表示,组间比较采用独立样本t检验。非正态分布数据(如主要和次要观察指标)用中位数(P_{25}, P_{75})表示。重复测量数据(术后抑郁HAMD-17、睡眠质量NRS及认知功能MMSE评分等)采用重复测量方差分析。

分类变量用例数(%)表示，组间比较采用χ^2检验或Fisher精确检验。P<0.05为差异有统计学意义。

2　结果

Esk组因中转开胸1例、病理结果为良性1例和家属拒绝电话随访1例，共排除3例。NS组因术后出血再次手术1例、肺叶楔形切除1例和病理结果为良性1例，共排除3例。最终，共获得82例患者的完整数据并纳入分析，每组各41例。

2.1　两组患者基线资料比较

两组患者在年龄、性别、BMI、ASA分级、合并症(高血压、糖尿病、冠心病)、受教育程度及术前1 d量表评分(HAMD-17、PSQI和MMSE)等方面差异无统计学意义(P>0.05)。见表1。

表 1　两组患者基线资料比较

Table 1　Comparison of baseline data between the two groups

Index	Esk group (n = 41)	NS group (n = 41)	P
Age/yr.	72 (69, 74)	72 (70, 74)	0.579
Sex			
Female	20 (48.8)	21 (51.2)	0.825
Male	21 (51.2)	20 (48.8)	0.825
BMI/(kg/m^2)	23 (21, 25)	23(21, 24)	0.140
ASA grade			
Ⅱ	16 (39.0)	21 (51.2)	0.187
Ⅲ	25 (61.0)	20 (48.8)	0.187
Comorbidities			
Hypertension	19 (46.3)	19 (46.3)	0.588
Diabetes	5 (12.2)	6 (14.6)	0.500
Coronary atherosclerotic heart disease	5 (12.2)	9 (22.0)	0.190
Educational attainment			
Primary school	6 (14.6)	5 (12.2)	0.500
Junior high school	21 (51.2)	19 (46.3)	0.825
Senior high school or above	14 (34.2)	17 (41.5)	0.519
Evaluation scores 1 day before surgery			
HAMD-17	6 (5, 7)	6 (5, 7)	0.778
PSQI	8 (7, 9)	8 (7, 9)	0.697
MMSE	27 (27, 28)	28 (26, 29)	0.522

BMI: body mass index; ASA: American Society of Anesthesiologists; HAMD-17: 17-item Hamilton Rating Scale for Depression; PSQI: Pittsburgh Sleep Quality Index; MMSE: Mini-Mental State Examination; Esk: esketamine; NS: normal saline. The data are presented as median (P_{25}, P_{75}) or case (%).

2.2　两组患者主要结局指标和次要结局指标比较

见表2。与NS组比较，Esk组患者术后7 d〔7(6, 8) d vs. 7(6, 12) d, P=0.045〕和30 d〔6(6, 7) d vs. 7(6, 9) d, P=0.020〕的HAMD-17评分降低；术后1 d、3 d和7 d的睡眠NRS评分降低(P<0.01)，MMSE评分升高(P<0.05)。

表 2　两组患者结局指标比较

Table 2　Comparison of outcome indicators between the two groups

Index	Esk group (n = 41)	NS group (n = 41)	P
Primary outcome			
HAMD-17 score			
7 d after surgery	7 (6, 8)	7 (6, 12)	0.045
30 d after surgery	6 (6, 7)	7 (6, 9)	0.020
Secondary outcomes			
Sleep quality			
1 d after surgery (NRS)	2 (1, 4)	4 (3, 6)	<0.001
3 d after surgery (NRS)	3 (2, 4)	4 (2, 5)	0.006
7 d after surgery (NRS)	2 (1, 4)	4 (2, 5)	0.002
30 d after surgery (PSQI)	8 (7, 11)	7 (9, 11)	0.566
MMSE score			
1 d after surgery	26 (23.5, 27)	23 (20, 26)	0.016
3 d after surgery	25 (23, 27)	24 (21, 25)	0.015
7 d after surgery	25 (23, 27.5)	24 (20, 26)	0.018
30 d after surgery	26 (25, 27)	26 (25, 27)	0.164

NRS: numeric rating scales; the other abbreviaions are explained in the note to Table 1. The data are presented as median (P_{25}, P_{75}).

2.3　两组患者其他指标比较

见表3。与NS组比较，Esk组术中丙泊酚、舒芬太尼、瑞芬太尼用量和呼气末七氟醚消耗量(切皮、手术30 min和手术60 min时)减少(P<0.05或<0.01)；术后呼吸机辅助时长、PACU停留时长及术后住院天数缩短(P<0.01)；两组间术中液体出入量及术中低血压、心动过速、心动过缓发生率、手术时长及病理类型差异均无统计学意义(P>0.05)。两组患者术中均未出现低氧血症或高血压。

2.4　两组患者安全性结果比较

见表4。与NS组比较，Esk组患者术后恶心/呕吐及痛觉过敏发生率降低(P<0.01)；两组患者术后24 h和48 h静息和咳嗽时疼痛NRS评分、皮肤瘙痒、头痛/头晕、幻觉/噩梦、躁动和苏醒延迟发生率差异均无统计学意义(P>0.05)。

2.5　两组患者分子生物学比较

见图1。与NS组比较，Esk组患者在T1 ~ T3时血清BDNF和5-HT浓度升高(P<0.05或<0.01)，S100β含量减少(P<0.01)；T1 ~ T2时血清NSE水平降低(P<0.01)。

表 3 两组患者其他指标比较

Table 3 Comparison of other indicators between the two groups

Index	Esk group (n = 41)	NS group (n = 41)	P
Anaesthetics and analgesics			
Propofol/mg	110 (85, 145)	140 (105, 155)	0.013
Sufentanil/μg	40 (35, 45)	50 (45, 50)	< 0.001
Remifentanil/mg	0.7 (0.5, 0.9)	1.0 (0.8, 1.0)	< 0.001
End-expiratory concentration of sevoflurane/%			
Skin incision	0.91 (0.76, 1.14)	1.19 (0.88, 1.62)	0.001
30 min of operation	0.84 (0.76, 0.94)	1.08 (0.97, 1.17)	< 0.001
60 min of operation	0.69 (0.60, 0.79)	0.98 (0.88, 1.09)	< 0.001
Fluid intake and outflow/mL			
Intraoperative fluid infusion	1 500 (1 150, 1 500)	1 500 (1 250, 1 500)	0.344
Intraoperative urine volume	300 (200, 400)	300 (200, 400)	0.965
Intraoperative blood loss	200 (100, 300)	200 (100, 300)	0.846
Intraoperative safety results			
Intraoperative hypoxemia	0	0	1.0
Intraoperative hypotension	1 (2.4)	0	0.500
Intraoperative hypertension	0	0	1.0
Intraoperative tachycardia	1 (2.4)	2 (4.8)	0.500
Intraoperative bradycardia	2 (4.8)	1 (2.4)	0.500
Length of surgery/min	110 (95, 125)	120 (100, 130)	0.165
Duration of postoperative ventilator assistance/min	36 (32, 40)	41 (36, 48)	< 0.001
Length of PACU stay/min	50 (45, 57)	55 (50, 60)	0.008
Length of postoperative hospital stay/d	5 (4, 6)	7 (5, 8)	0.001
Pathological diagnosis			
Adenocarcinoma	30 (73.2)	31 (75.6)	0.592
Squamous carcinoma	4 (9.8)	3 (7.3)	0.500
Others	7 (17.1)	7 (17.1)	0.615

PACU: postanesthesia care unit; the other abbreviaions are explained in the notes to Tables 1 and 2. The data are presented as median (P_{25}, P_{75}) or case (%).

表 4 两组患者安全性结果比较

Table 4 Comparison of safety outcomes between the two groups

Index	Esk group	NS group	P
Nausea or vomiting	7 (17.1)	18 (43.9)	0.008
0 to 24 h	7 (17.1)	12 (29.3)	0.148
Over 24 to 48 h	0	6 (14.6)	0.013
Pain scores at rest (NRS)			
At 24 h	2 (0, 2)	2 (0, 3)	0.729
At 48 h	0 (0, 1)	0 (0, 1)	0.944
Pain scores while coughing (NRS)			
At 24 h	3 (1, 4)	3 (1, 4)	0.529
At 48 h	1 (0, 2)	1 (0, 3)	0.669
Hyperalgesia	1 (2.4)	8 (19.5)	0.015
Pruritus	0	1 (2.4)	0.500
Headache or dizziness	3 (7.3)	2 (4.8)	0.500
Hallucination or nightmare	1 (2.4)	1 (2.4)	0.753
Agitation	0	1 (2.4)	0.500
Delayed recovery	0	0	1.0

The abbreviaions are explained in the notes to Tables 1 and 3. The data are presented as median (P_{25}, P_{75}) or case (%). n = 41 per group.

3 讨论

老年衰弱患者术后容易出现焦虑、抑郁、睡眠及认知功能障碍等心理精神问题，严重影响术后恢复质量，而术后抑郁、睡眠及认知功能障碍在一定程度上可增加患者衰弱发生率[23-24]。本研究主要通过应用艾司氯胺酮对胸腔镜下肺癌根治术老年衰弱患者进行干预，观察其对患者术后7 d和30 d的抑郁情况，以及术后1 d、3 d、7 d和30 d的睡眠质量及认知功能的影响。课题组主要通过量表评估患者抑郁情况、睡眠质量和认知功能，考虑到量表的主观性可能对研究结果产生影响，本研究检测了患者术后3 d血清生物学标志物。

抑郁症的发病机制尚不明确，目前主要认为与神经营养因子、单胺类神经递质、下丘脑-垂体-肾上腺激素轴及炎性细胞因子等有关[25]。本研究选择了目前认为与抑郁症发生及转归关系最为密切的BDNF和单胺类神经递

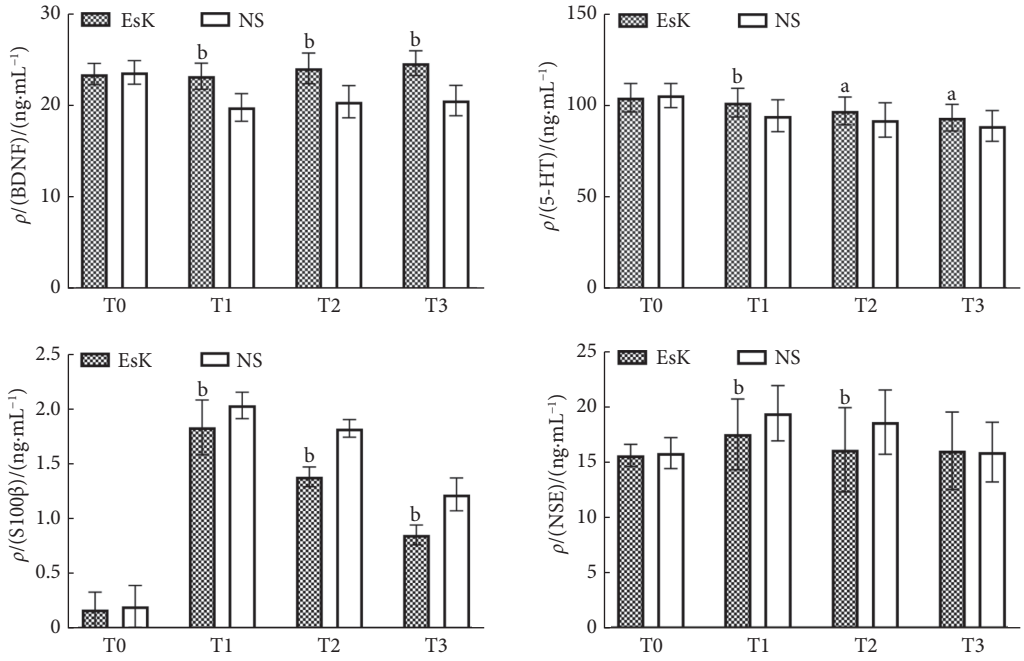

图 1　两组患者不同时间点血清BDNF、5-HT、S100β和NSE水平的比较

Fig 1　Comparison of serum BDNF, 5-HT, S100β, and NSE levels between the two groups at different time points

BDNF: brain-derived neurotrophic factor; 5-HT: 5-hydroxytryptamine; NSE: neuron-specific enolase. T0: before anesthesia induction; T1-T3: 24 h, 48 h, and 72 h after surgery. $^{a}P < 0.05$, $^{b}P < 0.01$, vs. NS group. $n = 41$ per group.

质5-HT作为血清生物学指标。BDNF是大脑中各种神经递质的重要调节因子，与抗抑郁作用关系极为密切。研究表明，抗抑郁药物可明显增加抑郁症患者脑中BDNF的表达[26-27]。5-HT主要分布于松果体和下丘脑，可参与睡眠、心理及精神状态的调节[28]。5-HT激动剂不但可以改善患者抑郁症状和大脑认知行为，还可以改善患者睡眠质量[29-30]。艾司氯胺酮对海马结构具有促神经可塑性作用，海马是艾司氯胺酮抗抑郁作用的关键区域[31]。但艾司氯胺酮抗抑郁的具体机制尚不明确。本研究显示，艾司氯胺酮干预后，患者术后7 d和30 d的HAMD-17评分及术后1 d、3 d和7 d的睡眠NRS评分明显降低，术后3 d内血清BDNF和5-HT水平明显升高。量表评分和生物学标志物检测结果均证实，艾司氯胺酮可以改善胸腔镜下肺癌根治术老年衰弱患者术后抑郁状态和睡眠质量。

患者术后认知功能障碍与众多因素相关，其中，高龄是一个重要的独立危险因素。胸腔镜下肺叶切除术老年患者术后认知功能障碍（POCD）的发生率高达26.7%[32]。POCD会严重影响患者术后恢复质量，甚至导致患者死亡。本研究量表结果显示，Esk组患者术后1 d和7 d的MMSE评分明显高于对照组。S100β蛋白和NSE是与POCD及脑功能关系最为密切的生物学标志物。史金麟等[33]研究证实，亚麻醉剂量艾司氯胺酮可改善胸腔镜肺叶楔形切除术老年患者术后认知功能。本研究结果显示，术后3 d内两组患者S100β蛋白和NSE浓度明显上升，艾司氯胺酮干预组患者术后3 d内血清S100β蛋白及术后2 d内NSE水平明显降低。结果表明，胸腔镜下肺癌根治术可对老年衰弱患者脑功能造成明显的损伤，而艾司氯胺酮可减轻这种损伤并改善患者术后早期认知功能。

此外，由于艾司氯胺酮可减少术中阿片类药物的应用，使患者术后恶心/呕吐及痛觉过敏发生率显著降低，这也是目前一些学者寻求少阿片化麻醉方式的一个重要原因[34-35]。同时，应用艾司氯胺酮可缩短患者术后呼吸机辅助时间、PACU停留时间及术后住院天数，这可能主要与术中镇痛、镇静等药物用量减少有关。结果显示，两组患者术后24 h和48 h静息和咳嗽时疼痛NRS评分均较低且没有明显差异，说明两组患者所采用的麻醉方式均能有效缓解患者术后疼痛。艾司氯胺酮可使术中相关麻醉药物的消耗量明显减少，说明艾司氯胺酮具有很强的镇痛、镇静作用，这也说明为何艾司氯胺酮是目前少阿片化麻醉的首选药物。

本研究也存在一定的不足。首先，本研究为单中心临床研究，且仅随访至术后30 d，后期课题组将进行多中心、大样本的前瞻性研究，并对患者抑郁情况、睡眠质量、认知功能、恢复质量及生存状态等进行远期随访，以观察艾司氯胺酮对患者远期并发症和结局的影响。其次，因神经组阻滞在胸腔镜手术中效果确切，可以降低许

多不良事件的发生率,所以本研究未设置单纯全麻组。

综上,艾司氯胺酮可改善胸腔镜下肺癌根治术老年衰弱患者术后抑郁状态、睡眠质量及认知功能,还可减少术中麻醉药物的消耗量、降低术后恶心/呕吐及痛觉过敏发生率、缩短术后呼吸机辅助时长、PACU停留时长及术后住院天数。

* * *

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