

# 脑深部电刺激术联合药物治疗原发性帕金森病疗效观察

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**【摘要】** **目的** 探讨脑深部电刺激术(DBS)联合药物治疗原发性帕金森病的有效性和安全性。**方法** 共 60 例原发性帕金森病患者分别予常规药物治疗(30 例)和脑深部电刺激术联合药物治疗(30 例),采用统一帕金森病评价量表(UPDRS)和帕金森病生活质量量表(PDQUALIF)评价病情严重程度和生活质量。**结果** DBS 组患者 UPDRS 量表之精神、行为和情绪( $P=0.023$ )、日常生活活动能力( $P=0.005$ )、运动功能( $P=0.025$ )和运动并发症( $P=0.008$ )以及 PDQUALIF 评分( $P=0.016$ )均低于对照组,治疗后 UPDRS 量表之精神、行为和情绪( $P=0.003$ )、日常生活活动能力( $P=0.016$ )、运动功能( $P=0.001$ )和运动并发症( $P=0.016$ )以及 PDQUALIF 评分( $P=0.000$ )亦低于治疗前。DBS 组总有效率[96.67%(29/30)]高于对照组[76.67%(23/30); $\chi^2=5.109, P=0.000$ ]。**结论** 脑深部电刺激术联合药物治疗原发性帕金森病可以有效改善临床症状,提高生活质量。

**【关键词】** 帕金森病; 深部脑刺激法; 药物疗法

## Clinical observation on the effect of deep brain stimulation combined with drug therapy in the treatment of idiopathic Parkinson's disease

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**【Abstract】** **Objective** To study the efficacy and safety of deep brain stimulation (DBS) combined with drug therapy in the treatment of idiopathic Parkinson's disease (PD). **Methods** From August 2013 to August 2015, 60 patients with idiopathic PD were enrolled. They were divided into DBS group (N=30) and control group (N=30) based on different treatment methods. The control group was given routine drug therapy, while DBS group was given DBS combined with drug therapy. Unified Parkinson's Disease Rating Scale (UPDRS) and Parkinson's Disease Quality of Life Scale (PDQUALIF) were used to evaluate the severity of disease and quality of life. **Results** In comparison with control group, UPDRS suggested lower mind, behavior and mood score ( $P=0.023$ ), lower activities of daily living score ( $P=0.005$ ), lower motor function score ( $P=0.025$ ), lower motor complications score ( $P=0.008$ ) and lower PDQUALIF score ( $P=0.016$ ) in DBS group. In comparison with scores in DBS group before treatment, UPDRS suggested lower mind, behavior and mood score ( $P=0.003$ ), lower activities of daily living score ( $P=0.016$ ), lower motor function score ( $P=0.001$ ), lower motor complications score ( $P=0.016$ ) and lower PDQUALIF score ( $P=0.000$ ) after treatment. Total effective rate was found higher in DBS group [96.67% (29/30);  $\chi^2=5.109, P=0.000$ ] than that in control group [76.67% (23/30)]. **Conclusions** DBS combined with drug therapy can effectively improve clinical symptoms and quality of life in patients with idiopathic PD.

**【Key words】** Parkinson disease; Deep brain stimulation; Drug therapy

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帕金森病(PD)是中老年人群常见的神经变性病,临床主要表现为静止性震颤、肌强直和运动迟缓等<sup>[1-4]</sup>,随病情进展可以导致运动障碍,晚期可以出现幻觉、妄想等精神障碍<sup>[5-7]</sup>。脑深部电刺激术(DBS)是治疗运动障碍性疾病的方法,具有疗效佳、手术安全、并发症发生率低等优点<sup>[8-9]</sup>,且术后可程控调节以治疗运动障碍。本研究比较脑深部电刺激术联合药物治疗与常规药物治疗原发性帕金森病的有效性和安全性,以期明确脑深部电刺激术的优势。

## 资料与方法

### 一、临床资料

1. 纳入标准 (1)原发性帕金森病的诊断参照国际运动障碍学会(MDS)2015年修订的临床诊断标准<sup>[10]</sup>:①不符合绝对排除标准。②至少存在2项支持标准,对多巴胺能药物有明确且显著的有效应答,即初始治疗期间,药物剂量增加症状明显改善,剂量减少症状明显加重[不包括轻微改变,统一帕金森病评价量表第三部分(UPDRS III)改善率>30%或主观感受],明确且显著的“开/关”期波动,以及某种程度上包括可预测的剂末现象;出现左旋多巴诱导异动症(LID);体格检查可见单侧肢体静止性震颤;存在嗅觉缺失或心肌<sup>131</sup>I-间碘苄胍(MIBG)PET提示心脏去交感神经支配。③无警示征象(red flags)。(2)年龄<75岁。(3)急性左旋多巴冲击试验(ALCT)证实运动症状(UPDRS III评分)改善率>30%。(4)头部MRI未见明显异常。(5)行手术治疗的患者,术中可配合测试、术后可配合程控。(6)本研究经河北医科大学第一医院道德伦理委员会审核批准,所有患者均自愿参加并签署知情同意书。

2. 排除标准 (1)非原发性帕金森病。(2)无症状波动的帕金森病。(3)伴严重的认知功能障碍和(或)严重的精神病。(4)一般状况欠佳,不能耐受或配合手术<sup>[11]</sup>。

3. 一般资料 选择2013年8月-2015年8月在河北医科大学第一医院诊断与治疗的原发性帕金森病患者共60例,男性49例,女性11例;年龄50~70岁,平均(62.36±10.25)岁;受教育程度5~20年,平均(10.68±3.73)年;病程2~10年,平均(5.26±1.65)年;入院时UPDRS评分60~140分,平均(98.25±26.52)分;帕金森病生活质量量表(PDQUALIF)评分40~105分,平均为(85.63±

表1 两组患者一般资料的比较

Table 1. Comparison of general data between 2 groups

Item	Control (N=30)	DBS (N=30)	$\chi^2$ or <i>t</i> value	<i>P</i> value
Sex [case (%)]			2.253	0.645
Male	24 (80.00)	25 (83.33)		
Female	6 (20.00)	5 (16.67)		
Age ( $\bar{x} \pm s$ , year)	61.95 ± 10.94	62.38 ± 9.92	2.324	0.845
Education ( $\bar{x} \pm s$ , year)	10.85 ± 2.45	10.43 ± 2.25	2.125	0.735
Duration ( $\bar{x} \pm s$ , year)	7.16 ± 0.75	6.96 ± 0.73	2.253	0.852
UPDRS ( $\bar{x} \pm s$ , score)	99.46 ± 25.35	97.86 ± 28.36	2.265	0.853
PDQUALIF ( $\bar{x} \pm s$ , score)	86.45 ± 32.23	84.24 ± 29.73	2.253	0.654

$\chi^2$  test for comparison of sex, and two-independent-sample *t* test for comparison of others. DBS, deep brain stimulation, 脑深部电刺激术;UPDRS, Unified Parkinson's Disease Rating Scale, 统一帕金森病评价量表;PDQUALIF, Parkinson's Disease Quality of Life Scale, 帕金森病生活质量量表

30.75)分。根据患者自愿原则分为单纯药物治疗组(对照组)和脑深部电刺激术联合药物治疗组(DBS组)。(1)对照组:30例患者,男性24例,女性6例;年龄54~75岁,平均为(61.95±10.94)岁;受教育程度5~19年,平均(10.85±2.45)年;病程2~10年,平均(7.16±0.75)年;入院时UPDRS评分55~145分,平均(99.46±25.35)分;PDQUALIF评分39~105分,平均为(86.45±32.23)分。(2)DBS组:30例患者,男性25例,女性5例;年龄55~75岁,平均为(62.38±9.92)岁;受教育程度5~20年,平均为(10.43±2.25)年;病程2~10年,平均(6.96±0.73)年;入院时UPDRS评分62~140分,平均(97.86±28.36)分;PDQUALIF评分为42~105分,平均为(84.24±29.73)分。两组患者一般资料比较,差异无统计学意义(均 $P>0.05$ ,表1),具有可比性。

### 二、研究方法

1. 治疗方法 (1)对照组:30例患者均予以吡贝地尔缓释片联合左旋多巴治疗。吡贝地尔缓释片[规格:50 mg/片,施维雅(天津)制药有限公司]150 mg/d口服,左旋多巴(规格:250 mg/片,上海罗氏制药有限公司)750 mg/d口服,连续治疗6个月。(2)DBS组:30例患者均于手术当日停用抗帕金森病及其他抗肌张力障碍药物,坐位或上半身抬高仰卧位,于局部麻醉下安装立体定位头架[医科达(上海)医疗器械有限公司],行高场强(3.0T)MRI(美国GE公司)扫描,所获得的图像导入Leksell SurgiPlan

手术计划系统(瑞典 Elekta 公司),重建头部三维影像并计算刺激靶点坐标。以微推进器将微电极向靶点方向推进,根据神经电生理学监测获得的波形和背景噪声变化,以及术中临时刺激效果,最终定位靶点为丘脑底核(STN)、苍白球内侧部(GPi)和丘脑腹中间核(Vim)<sup>[12]</sup>。刺激电流经圆柱形电极触点传输,电极触点直径 1.27 mm、长度 1.50 mm、表面积 5.99 mm<sup>2</sup>。经体外遥控监测以调节刺激参数,电压 0~3 V、脉宽 60~90  $\mu$ s、频率 150~185 Hz。于全身麻醉下植入脉冲发生器,术后 3~4 周以测试时未出现不良反应的最佳刺激参数开启刺激器,进行持续电刺激。患者意识恢复后 1 h 予以吡贝地尔缓释片 50 mg/d 和多巴丝肼(美多芭)375 mg/d 口服 6 个月。

2. 疗效评价 所有患者均于治疗后 6 个月采用 UPDRS 量表评价治疗效果和 PDQUALIF 量表评价生活质量。UPDRS 量表包括精神、行为和情绪,日常生活活动能力,运动功能和运动并发症等项内容,每项评分 60 分,评分越高、病情越严重。PDQUALIF 量表包括社会功能和角色、自我形象、两性关系、睡眠、世界观、身体健康、自理能力和排尿功能共 8 个方面 33 项内容,每项评分 0~5 分,总评分 128 分,评分越低、生活质量越好。疗效判断标准:显效,治疗后运动功能明显改善,可进行日常活动和工作,且 UPDRS 评分减少 > 30%;有效,治疗后运动功能改善,可进行简单活动、但不能工作,且 UPDRS 评分减少 > 10%~30%;无效,治疗后运动功能无变化或加重,无法正常活动或工作,且 UPDRS 评分减少  $\leq$  10%。显效和有效为总有效,计算总有效率,总有效率(%)=(显效例数+有效例数)/总例数 $\times$ 100%。

3. 统计分析方法 采用 SPSS 22.0 统计软件进行数据处理与分析。计数资料以相对数构成比(%)或率(%)表示,采用  $\chi^2$  检验。计量资料以均数 $\pm$ 标准差( $\bar{x} \pm s$ )表示,采用两组独立样本的  $t$  检验;两组患者治疗前后 UPDRS 评分和 PDQUALIF 评分的比较采用前后测量设计的方差分析。以  $P \leq 0.05$  为差异具有统计学意义。

## 结 果

DBS 组患者 UPDRS 量表之精神、行为和情绪( $P = 0.023$ )、日常生活活动能力( $P = 0.005$ )、运动功能( $P = 0.025$ )和运动并发症( $P = 0.008$ )均低于对照组,治疗后精神、行为和情绪( $P = 0.003$ )、日常生活

活动能力( $P = 0.016$ )、运动功能( $P = 0.001$ )和运动并发症( $P = 0.016$ )亦低于治疗前(表 2, 3),表明药物治疗后患者临床症状明显改善,脑深部电刺激术联合药物治疗效果更佳。DBS 组患者 PDQUALIF 评分低于对照组( $P = 0.016$ ),治疗后亦低于治疗前( $P = 0.000$ ;表 4, 5),表明药物治疗后患者生活质量明显改善,脑深部电刺激术联合药物治疗效果更佳。

DBS 组患者显效 20 例(66.67%)、有效 9 例(30%)、无效 1 例(3.33%),总有效率为 96.67%(29/30);对照组患者显效 13 例(43.33%)、有效 10 例(33.33%)、无效 7 例(23.33%),总有效率为 76.67%(23/30)。两组总有效率比较,差异具有统计学意义( $\chi^2 = 5.109, P = 0.000$ )。

## 讨 论

脑深部电刺激术开始于 20 世纪 50~70 年代,1947 年,Spiegel 等<sup>[13]</sup>尝试采用电刺激术和高频电凝术治疗帕金森病,以及丘脑底核脑深部电刺激术治疗慢性头痛<sup>[14-15]</sup>,后来也有用于痉挛、小脑麻痹、癫痫等治疗的尝试。法国 Benabid 等<sup>[16]</sup>于 1991 年以及 Blond 和 Siegfried<sup>[17]</sup>于 1994 年分别报告丘脑底核脑深部电刺激术治疗震颤的安全性和有效性。相对于传统毁损术,脑深部电刺激术具有可调节、并发症少等特点。脑深部电刺激术于 1997 年获得美国食品与药品管理局(FDA)临床应用认证,于 1998 年开始在国内开展,首都医科大学附属北京天坛医院神经外科进行首例脑深部电刺激术治疗帕金森病例,迄今脑深部电刺激术已在我国开展 18 年。随着国内神经影像学、神经电生理学和生物工程学等相关学科的发展,脑深部电刺激术在运动障碍性疾病外科治疗中的技术水平和应用也得到迅速提高,并已证明是目前中晚期帕金森病患者的有效治疗方法。脑深部电刺激术的作用机制目前尚未完全阐明,推测神经元受到刺激后可以产生不同效应,这种效应与电刺激的特性存在一定关系<sup>[18]</sup>,从而发挥平衡神经元电冲动的作用,降低其过度兴奋性,从而缓解静止性震颤、肌强直或异动症等<sup>[19]</sup>。同时还应注意手术相关并发症,本研究仅 1 例患者出现头痛,但颅内出血、癫痫发作、感染、电极移位等均可能是手术相关并发症<sup>[20]</sup>。术前由具有丰富临床经验的手术团队进行详细评估,术后在帕金森病专病门诊进行严密观察、随访并调整药物及其剂量,最大程度地减少手术相关并发症。

**表 2** 两组患者治疗前后 UPDRS 评分的比较( $\bar{x} \pm s$ , 评分)

**Table 2.** Comparison of UPDRS scores between 2 groups before and after treatment ( $\bar{x} \pm s$ , score)

Group	N	Before treatment	After treatment	Group	N	Before treatment	After treatment
Mind, behavior and mood				Motor function			
Control	30	6.93 ± 2.95	5.38 ± 1.96	Control	30	54.25 ± 3.27	39.98 ± 2.85
DBS	30	6.95 ± 3.28	3.36 ± 2.53	DBS	30	57.98 ± 3.84	28.91 ± 2.46
ADL				Motor complication			
Control	30	24.92 ± 3.29	15.37 ± 3.45	Control	30	15.23 ± 4.16	10.32 ± 2.85
DBS	30	24.38 ± 22.90	10.96 ± 2.83	DBS	30	14.93 ± 4.58	8.83 ± 3.26

DBS, deep brain stimulation, 脑深部电刺激术; ADL, activities of daily living, 日常生活活动能力

**表 3** 两组患者治疗前后 UPDRS 评分的前后测量设计的方差分析表

**Table 3.** ANOVA of pretest-posttest design for UPDRS scores of 2 groups before and after treatment

Source of variation	SS	df	MS	F value	P value	Source of variation	SS	df	MS	F value	P value
Mind, behavior and mood						Motor function					
Treatment	865.126	3	433.659	25.654	0.023	Treatment	875.559	3	639.165	15.249	0.025
Time	165.245	2	125.122	8.528	0.003	Time	643.546	2	265.682	5.323	0.001
Treatment × time	124.543	6	65.585	42.625	0.000	Treatment × time	245.265	6	165.485	95.276	0.000
Error between groups	86.338	27	45.387			Error between groups	106.614	27	85.456		
Error within group	20.349	52	8.636			Error within group	65.593	52	28.603		
ADL						Motor complication					
Treatment	1062.540	3	805.152	25.587	0.005	Treatment	1549.652	3	133.580	23.587	0.008
Time	155.322	2	75.681	5.678	0.016	Time	745.585	2	691.562	9.528	0.016
Treatment × time	94.668	6	65.490	35.568	0.000	Treatment × time	425.476	6	267.623	127.528	0.006
Error between groups	76.452	27	35.487			Error between groups	226.698	27	62.675		
Error within group	28.653	52	10.235			Error within group	58.685	52	30.236		

ADL, activities of daily living, 日常生活活动能力

**表 4** 两组患者治疗前后 PDQUALIF 评分的比较( $\bar{x} \pm s$ , 评分)

**Table 4.** Comparison of PDQUALIF before and after treatment between 2 groups ( $\bar{x} \pm s$ , score)

Group	N	Before treatment	After treatment
Control	30	86.45 ± 32.23	55.32 ± 14.16
DBS	30	84.24 ± 29.73	40.28 ± 13.15

DBS, deep brain stimulation, 脑深部电刺激术

**表 5** 两组患者治疗前后 PDQUALIF 评分的前后测量设计的方差分析表

**Table 5.** ANOVA of pretest - posttest design for PDQUALIF score of 2 groups before and after treatment

Source of variation	SS	df	MS	F value	P value
Treatment	665.563	3	482.782	15.652	0.016
Time	338.356	2	228.363	3.563	0.000
Treatment × time	125.482	6	65.758	28.135	0.000
Error between groups	136.259	27	35.380		
Error within group	153.485	52	12.652		

脑深部电刺激术可以直接改善帕金森病静止性震颤、肌强直和运动迟缓三大典型症状<sup>[21]</sup>, 术后左旋多巴剂量显著减少, 从而减轻药物不良反应。本研究帕金森病患者行脑深部电刺激术后药物剂量明显减少, 临床症状有效缓解。鉴于其可调节性和安全、有效的特点, 脑深部电刺激术是治疗中晚期帕金森病的较好选择<sup>[22-24]</sup>。

刘畅等<sup>[25]</sup>对颅脑创伤(TBI)后肌张力障碍患者

予脑深部电刺激术治疗, 术后 Burke-Fahn-Marsden 肌张力障碍量表(BFMDRS)运动障碍和功能障碍评分降低, 临床症状明显改善, 表明脑深部电刺激术对运动障碍性疾病具有较好疗效。曹雄彬等<sup>[26]</sup>采用脑深部电刺激术治疗帕金森病运动障碍, 术后临床症状得到有效改善。本研究比较常规药物治疗与脑深部电刺激术联合药物治疗原发性帕金森病的效果, 结果显示, 脑深部电刺激术联合药物治疗

患者 UPDRS 和 PDQUALIF 评分均低于常规药物治疗组,治疗后两项评分均低于治疗前;脑深部电刺激联合药物治疗的总有效率为 96.67%(29/30),高于常规药物治疗的 76.67%(23/30)。值得注意的是,进行脑深部电刺激术并不意味着完全停药,而是明显减少药物剂量,从而有效控制患者症状波动、异动症等,改善生活质量。

综上所述,帕金森病及运动障碍性疾病患者进行脑深部电刺激术可以有效改善临床症状,缓解精神状态,减少药物不良反应,提高生活质量。

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## ***Encyclopedia of Computational Neuroscience published***

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