

Review Article

Comparison of Subthalamic Nucleus and Globus Pallidus Deep Brain Stimulation in Parkinson's Disease: A Systematic Review

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Abstract

Background: Deep Brain Stimulation (DBS) is regarded as a viable therapeutic choice for Parkinson's Disease (PD). The two most common sites for DBS are the Subthalamic Nucleus (STN) and Globus Pallidus (GPI). In this study, the clinical effectiveness of these two targets was compared.

Methods: A systematic literature search in electronic databases were restricted to English language publications 2010 to 2021. Specified MeSH terms were searched in all databases. Studies that evaluated the Unified Parkinson's Disease Rating Scale (UPDRS) III were selected by meeting the following criteria: (1) had at least three months follow-up period; (2) compared both GPI and STN DBS; (3) at least five participants in each group; (4) conducted after 2010. Study quality assessment was performed using the Modified Jadad Scale.

Results: 3577 potentially relevant articles were identified 3569 were excluded based on title and abstract, duplicate and unsuitable article removal. Eight articles satisfied the inclusion criteria and were scrutinized (458 PD patients). Majority of studies reported no statistically significant between-group difference for improvements in UPDRS III scores.

Conclusions: Although there were some results in terms of action tremor, rigidity, and urinary symptoms, which indicated that STN DBS might be a better choice or regarding the adverse effects, GPI seemed better; but it cannot be concluded that one target is superior. Other larger randomized clinical trials with longer follow-up periods and control groups are needed to decide which target is more efficient for stimulation and imposes fewer adverse effects on the patients.

Keywords: Deep Brain stimulation; Globus pallidus; Parkinson's disease; Subthalamic nucleus; UPDRS

Introduction

Parkinson's disease is the most common movement disorder, the second common progressive, disabling, and neurodegenerative disease, which is expected to be as prevalent as 12.9 million cases by 2040 [1-4]. Although acute diseases such as stroke are decreased in developed countries, neurodegenerative diseases are increasing and affecting most of their population [5]. PD prevalence is estimated at 160 per 100000 in individuals over 65 years old [6]. Parkinson's disease is characterized by slow movements, rigidity, and low amplitude movements without the previous automaticity. Gait problems are among the most prominent and disabling signs of this disorder which progress as time passes [7]. Various genetic, environmental, lifestyle-related factors and aging have been proposed as the triggers for Parkinson's disease initiation [8,9]. Classically, Parkinson's disease is attributed to the progressive death of dopaminergic neurons of basal ganglia and hyperactivity of striatopallidal pathway in the dorsal striatum due to loss of dopamine signaling and presence of Lewy bodies and Lewy neuritis. PD patients suffer from various motor and non-motor symptoms that negatively impact their daily lives [10]. Levodopa, a dopamine precursor, was developed for the first time in 1911 [11]. It has been used as an efficacious drug for PD treatment for

over 50 years, but it has been shown that its efficacy declines as the disease progresses [6,12]. Surgical treatment of movement disorders started in 1987 by targeting the ventral intermediate nucleus of the thalamus [13,14] by the DBS technique. DBS is a common and effective surgical treatment option that alleviates motor symptoms. It was introduced about three decades ago and is recently performed on several new targets in the brain, including the Subthalamic nucleus (STN) and Globus Pallidus internus (GPI) [10,15,16]. Performing this technique on the STN and GPI has proven to be highly effective and safe, but several adverse effects like verbal fluency problems are reported. This is attributed to the stimulation site in some studies [17]. This systematic review investigated the efficacy of STN and GPI deep brain stimulation on UPDRS score outcomes in Parkinson's disease and its related adverse effects.

Methods**Search plan**

Potentially relevant English-language articles, published from 2010 to 2021, were recognized by searching in Embase, Cochrane Library, and PubMed databases. We searched for studies including both targets (GPI and STN) and their related aspects. Search terms

were deep brain stimulation (DBS) [MeSH term] or in combination with the following keywords: Controlled Clinical Trial [Publication Category], Randomized Controlled Trial [Publication Category], Globus Pallidus internus [MeSH term], Globus Pallidus [MeSH term], GPi [MeSH term], Subthalamic nucleus [MeSH term], STN [MeSH term], and Parkinson's disease [MeSH term].

Study selection criteria

For this research, we included the clinical studies that (1) contained evaluated unified PD rating scale (UPDRS) III before and after deep brain stimulation; (2) compared GPi-DBS and STN-DBS for PD; (3) recruiting more than five subjects in GPi and STN groups; (4) had a description of adverse events; (5) had more than three months of follow-up period; (6) Availability of English full text (7). The selection process took place in two phases: 1) title and the abstract selection; 2) full-text selection. These processes were done by all researchers independently. The full texts of the articles were ordered and compared according to the eligibility criteria. Any disagreements were resolved by discussion.

Data collection

The database was created by gathering the data about study design, efficacy, symptoms, materials, and population. Additionally, different adverse events and UPDRS III scores were extracted from articles.

Results

In total, 3577 potentially related articles were identified from the following databases: 834 studies from Embase, 676 studies from Cochrane Library, and 2067 studies from PubMed. After the primary evaluation, studies with unsuitable titles and abstracts were excluded (3461), duplicate articles were removed (102), 14 articles remained for further assessment.

Two systematic reviews [18,19], two meta-analysis [20,21], and two letters [22,23] were also removed. The full texts of the remaining eight articles were scrutinized (Figure 1).

Study characteristics

The features of the Eight studies evaluated in this meta-analysis are shown in Table 1. This study included 485 PD patients (226 in the GPi group and 259 in the STN group). The mean and SD age of GPi group participants was 54 ± 4.51 to 64.26 ± 8.79 years old, and STN group participants were 56.16 ± 9.6 to 66.5 ± 7.02 years old. The duration of follow-up varied from six months to 36 months. Two studies were conducted in the USA [34,35], two studies in Europe [36,37], and four studies in Asia [38-41].

Quality assessment process

Although there was no requirement for designating quality threshold level rather than the inclusion criteria, the validity of studies was evaluated by Modified Jadad scale [42,43]. Data are demonstrated in Table 2. According to the Jadad scale, the majority of included studies had low evidence quality. In detail, only two studies [36,37] received four scores showing moderate-quality evidence. One study [41] scored 3 points, three studies [34,35,40] scored 2 points, and two studies [38,39] scored 1 point, all showing low evidence quality.

Findings of a systematic review of included studies

Odekerken et al. demonstrated that the change in UPDRS

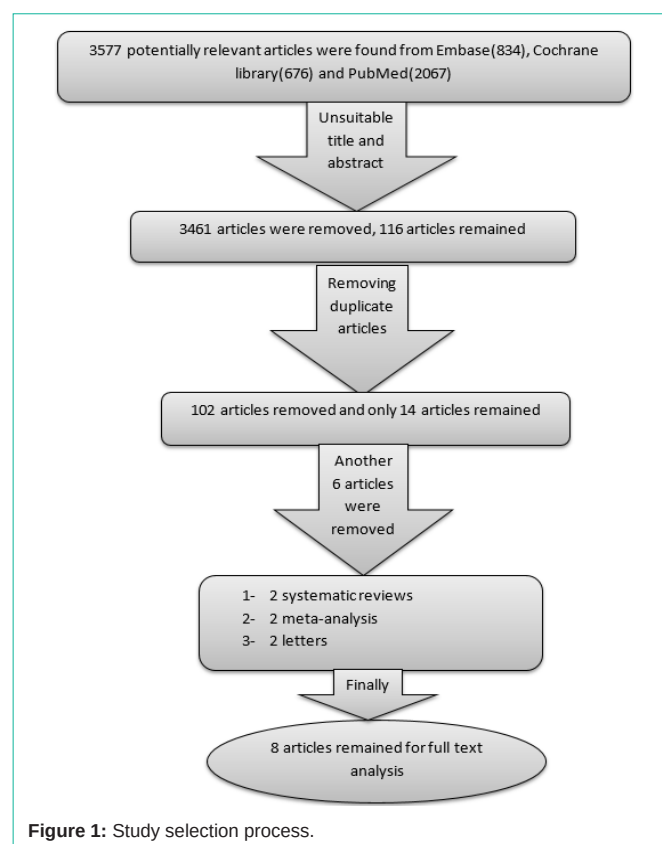


Figure 1: Study selection process.

score during the off-phase was lower in the GPi group than in the STN group, and during the on-phase, dyskinesia was less in the GPi group compared to the STN group. In both on-phase and off-phase, the reduction in time was similar, but it was significant only in the off-phase ($p=0.02$) [26]. Troche et al. showed there was a significant improvement in UPDRS score at off-medication state before and after surgery for both groups ($p < 0.001$). This is also true about comparing UPDRS on medication before surgery to UPDRS on medication and on stimulation after surgery ($p=0.038$) [28]. In another study conducted by Odekerken et al., more improvements were reported the off-drug phase UPDRS-ME score after three years in the STN group ($p=0.04$ while no between-group differences were shown in the on-drug phase) [27]. In the study of Gong et al., four months after DBS, all patients experienced improvement ($\geq 30\%$) in UPDRS score in off-period, and pain symptoms improvement rate was $79 \pm 27\%$ and $75 \pm 27\%$ in STN and GPi groups, respectively [29]. Fan et al. demonstrated that in the drug off-phase, the mean improvement of UPDRS was 41.50% and 43.56% in STN and GPi groups, respectively, with no significant difference between the group ($p=0.609$).

Additionally, GPi DBS had direct anti-dyskinesia effects (30). Wong et al. proved that STN DBS was related to a statistically significant decrease in bradykinesia and rigidity after six months compared with GPi DBS ($p < 0.001$ and $p=0.025$, respectively). However, there was no significant between group differences in terms of tremor outcomes. [24]. Celiker et al. reported on-phase UPDRS motor scores were significantly declined in both STN and GPi groups ($p < 0.05$), while STN DBS was better in improving bladder symptoms. In addition, both groups had fewer sleep problems after

Table 1: Main characteristics of studies included in this review.

	Reference	Target	Age	Sample Size	UPDRS on-Period- Baseline	UPDRS off-Period- Baseline	Follow Up Period (Month)	Place
1	Odekerken [36]	GPI	59.1±7.8	62	16±8	43.8±13.5	12	Europe
		STN	60.9±7.6	63	17±9.9	44.4±15.5		
2	Troche [38]	GPI	64.26±8.79	19	23.13±6.73	39.89±11.06	6	Asia
		STN	66.5±7.02	14	23.43±10.64	35.93±8.98		
3	Odekerken [37]	GPI	59.1±7.8	43	NA	43	36	Europe
		STN	60.9±7.6	47		41		
4	Gong [39]	GPI	63.2±9.1	28	26.2±7.5	NA	4	Asia
		STN	62.3±10.4	36	29.0±10.0			
5	Fan [40]	GPI	60.43±8.44	23	NA	50.68±15.36	18.26±8.38	Asia
		STN	59.65±9.11	20		47.85±14.95	21.60±8.79	
6	Celiker [41]	GPI	54±4.51	6	22.50±6.65	49.00±13.57	24	Asia
		STN	56.16±9.6	6	22.16±6.55	47.00±14.01		
7	Okun [35]	GPI	60.1±5.5	14	20.8±8.68	40.5±11.2	12	USA
		STN	58.0±10.7	16	21.3±7.56	41.2±9.32		
8	Wong [34]	GPI	63±8.12	31	NA	47.32±11.79	12	USA
		STN	61±10.33	57		44.12±10.45		

Table 2: Modified Jadad Scale rating.

Study	Point for randomization	Point for an appropriate method of randomization	Point for blinding	Point for an appropriate method of blinding	Point for a description of withdrawals	Point for a description of inclusion/exclusion criteria	Total score
Odekerken [36]	1	1	0	0	1	1	4
Troche [38]	0	0	0	0	0	1	1
Odekerken [37]	1	0	1	0	1	1	4
Gong [39]	0	0	0	0	0	1	1
Fan [40]	1	0	0	0	0	1	2
Celiker [41]	1	0	1	0	0	1	3
Okun [35]	1	0	0	0	1	0	2
Wong [34]	0	0	0	0	1	1	2

the surgery [31]. Okun et al. investigated the effect of unilateral and staged bilateral STN and GPI DBS. They found that off phase UPDRS motor scores, in both unilateral and staged bilateral modes, improved significantly after four and 12 months follow-up [25].

Adverse events

Odekerken et al. reported no statistically significant difference between groups in terms of adverse events ($p>0.05$) [36]. Troche et al. showed that mean penetration-aspiration (PA) scores did not change significantly for participants who received GPI surgery ($p=0.857$) but significantly worsened for participants who received STN DBS ($p=0.007$) and STN DBS have an adverse effect on swallowing function. In contrast, unilateral GPI DBS does not have this deleterious effect [38]. Fifty percent of patients in the STN group in the study of Fan et al. had dyskinesia caused by stimulation. In ten of these patients, the direct anti-dyskinesia effect of STN DBS was also noticed [40]. Okun et al. reported only minor mood and apathy effects, which were not significant [35]. In another study carried out by Odekerken et al., no significant differences were reported in terms of adverse events for the two groups; only minor events were reported [37]. Wong et al. found that the most common adverse events were

problems with DBS lead hardware and hemorrhage, which were minor and controlled easily [34].

Discussion

As a surgical technique, DBS has gained wide popularity in treating patients with advanced Parkinson's disease. In this review, the UPDRS III score and adverse events were evaluated to measure the outcomes after GPI DBS or STN DBS as common targets.

Tremor is an important sign of PD and its pathogenesis is attributed to the disruption of the cerebello-thalamo-cortical pathway. It has been shown that GPI has a role in tremor pathogenesis too, and its stimulation could even trigger tremor through its efferent fibers because of stimulation spread into the pallido-thalamic outflow fibers [24]. The practical difference of STN and GPI in terms of tremor is mainly because of their distinct connectivities in the tremor circuit, where STN has afferent and efferent connections with cerebello-thalamo-cortical network and GPI has only efferent connections [24]. The better control of resting tremor in the dorsal STN DBS can be because of dentato-rubro-thalamic fibers modulation in the posterior sub-thalamic region or relation of fibers to motor and

premotor cortex, while assessment of action tremor did not reveal any relation with specific region [24]. Direct anti-dyskinesia effects of STN DBS were exerted by stimulation of the area above STN where pallidothalamic, pallidosubthalamic and subthalamopallidal fibers are present [30]. Wong et al. found that in the short term, first six months after surgery, for rigidity, tremor and bradykinesia, STN-DBS had much more positive effects than GPi-DBS. They evaluated tremor according to UPDRS3 (item 21), which combines postural and kinetic tremor, and it cannot differentiate between re-emergent postural tremor and pure kinds of them [24]. Additionally, the GPi dyskinesia reduction effect was better than STN in the onphase, but this result was thought to be an artefact of the study design since patients in the STN DBS group had less severe dyskinesias than the standard assessments, and they took less medication than the GPi group in their regular life. Meanwhile all patients received the same amount of Levodopa as the baseline amount [26,27]. STN-DBS decreases detrusor hyperreflexia and increases bladder capacity via modulation of bladder afferents and central sensory processing, while the impact of GPi on urinary problems is not well understood [31]. Additionally, sleep-related problems such as insomnia, daytime sleepiness, and restless legs are common in Parkinson's disease patients. It has been shown that STN-DBS has a role in improving the objective polysomnographic features of sleep quality, which may be due to the resolution of motor symptoms and not the effect on the sleep center [31]. Regarding the adverse events, the reason for fewer complications of Globus pallidus in swallowing motor function is not clearly known, but it can be attributed firstly to reciprocal connections between pedunculo pontine nucleus (PPN) and Gpi or STN. GPi has an inhibitory effect on it, and STN has excitatory effects, and secondly the theory that patients who received STN DBS did not respond well like those who underwent GPi DBS [28]. Several studies had short follow-up periods, so determining the long-term efficiency of DBS in PD patients' needs studies with more follow-up duration.

In addition, to assess the effect of medications and DBS on pain symptoms, a control group should be considered in future studies. The study conducted by Fan et al. was retrospective, and it is clear that randomized controlled trials are much better for these kinds of research [30]. In longitudinal studies, like the studies in this review, the follow-up period is important because there will be dropouts due to different reasons. In the study conducted by Odekerken et al., at the third year of their follow-up, the sample size was 70 percent of the baseline cohort (there were withdrawals in the follow-up period). However, the sample size of the study was considered suitable for statistical analysis [27]. The findings of this study must be interpreted cautiously. It can be generally hypothesized, but not definitely stated, that STN-DBS and GPi-DBS are both suitable stimulation sites. However, STN had better outcomes regarding urinary symptoms, pain, dyskinesia, and action tremor. The main limitation of this systematic review study was moderate to low quality of the included studies (according to the Modified Jadad scale).

Conclusion

According to the results of this systematic review, although STN was better in terms of improving action tremor, and GPi was related to less adverse events in the studies, it cannot prove the superiority of any of the two targets. It is clear that more and more clinical trials with large sample size, longer follow-up periods and more specific

outcome assessments are needed to conclude which target is definitely better.

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