VIEWPOINT

Does Deep Brain Stimulation of the Subthalamic Nucleus Prolong Survival in Parkinson's Disease?

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Parkinson's disease (PD) is associated with increased mortality, which has not changed much after the introduction of levodopa.[1-3] According to a recent study, however, mortality rates in idiopathic PD are increased only moderately, with a reduction in life expectancy of about 1 year when compared with the general population (hazard ratio = 1.75; 95% confidence interval, 1.39-2.21).[4]

During the past decades, deep brain stimulation (DBS) of the subthalamic nucleus (STN) has emerged as an effective treatment for drug-resistant resting tremor and disabling drug-induced motor complications in patients with PD. Growing data show an improvement of motor symptoms and quality of life in PD patients during a period of up to 5 years after DBS.[5] The few available studies with longer follow-up periods (8-10 years), show a persistent effect on dopaminergic motor symptoms, although axial symptoms (gait, speech, postural stability) and nonmotor symptoms (eg, cognitive function) deteriorate. Data on the quality of life in follow-up for more than 5 years are scanty.[6-11]

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It is hitherto still unclear whether STN DBS improves the survival of patients with PD. Several studies reported on survival of PD patients after DBS,[10,12,13] but only 3 studies used a control group and are therefore potentially informative of a survival difference between patients who did or did not undergo STN DBS.[14-16] One of these studies found no significant difference in survival in the DBS group in comparison with a PD control group derived from a population-based control series.[14] As a result of the study design and the inclusion criteria used, biases in favor of the control group cannot be excluded. Indeed, patients were included if they were still alive after the inclusion period of 4 years and had completed 2 motor examinations, which led to the exclusion of 81 patients who had already died in the control group, as opposed to only 2 patients in the DBS group. In addition, important data such as disease duration at baseline or age at onset were not reported. Two other studies reported longer survival in the DBS group.[15,16] In one study, the control group included patients who were deemed eligible for surgery but decided to continue medical treatment.[15] The 2 patient groups did not show significant differences at baseline concerning age, gender, ethnicity, disease duration, amount of medication, or preexisting diagnosis of depression. Even after adjusting for potential confounding factors, patients undergoing STN DBS showed significantly longer survival (hazard ratio = 0.29; 95% confidence interval, 0.13-0.64; $P = .002$) and were significantly less likely to be admitted to a residential care home (odds ratio = 0.1; 95% confidence interval, 0.0-0.3; $P < .001$) than those managed purely medically. Although this is a convincing study, some uncertainties remain because the control group was relatively small (41 patients), and the fact that patients in the control group refused surgery could theoretically by itself introduce some bias. In addition, relevant information on comorbidity, baseline UPDRS score, and cognition was not available. The most recent study[16] involved a large, multicenter cohort study of 611

veterans with PD who received DBS and were retrospectively propensity-score matched to a cohort of 611 veterans with PD who were only medically managed. The results showed a survival advantage of approximately 7.6 months for patients with DBS (2291 vs 2063 days; hazard ratio = 0.69; 95% confidence interval, 0.56-0.85). It must be noted that, comparable to other methods aiming to resolve confounding problems in causal inference, the propensity score approach has its limitations.[17] The justification of using a propensity score approach is evidently dependent on the availability of information on the individual and contextual confounders. Unfortunately, the authors had no information on age at onset, disease duration, and disease stage at the index date. More important, they had also no information on the severity of motor (including postural instability, freezing, and speech) and nonmotor symptoms (including cognitive function and psychiatric symptoms). Most of these symptoms that are often considered as exclusion criteria for DBS and negatively affect survival[18,19] will inevitably occur more frequently in the control group, thus favorably affecting survival in the DBS cohort. In addition, although on one hand DBS may have been offered to patients in more advanced stages of the disease (with negative consequences for survival of the DBS cohort), on the other hand surgery is usually withheld to patients who are too advanced in their disease to benefit from the procedure or have other comorbidities (with negative consequences for survival of the medically managed cohort).

Despite the use of large cohorts and attempts to match groups properly, it is of note that the selection procedure for DBS involves some intrinsic biases that cannot be avoided, if not in a randomized controlled trial of sufficient sample size, in which patients are recruited from the same population, in the same time period, and where the follow-up is sufficiently long. Such a trial in patients with advanced PD is probably unethical and not feasible given the demonstrated superiority of DBS in improving the quality of life of selected patients as compared to best medical treatment, at least in the short to medium term.

Nevertheless, although the evidence thus far is not fully conclusive, the data that are available seem to point to some increased survival in favor of DBS. This survival benefit may potentially be attributed to improved motor control in DBS patients, which may in turn positively influence general health, for example, by restoration of weight loss, better swallowing and respiratory functions, and more efficient personal care. The results of 1 study indeed showed that a significantly lower proportion of DBS patients died of respiratory causes in comparison with medically managed patients,[15] although this difference was not found in another study.[16]

Alternatively, increased survival after STN DBS might also point to a direct effect of stimulation on the disease course. The suggestion of neuroprotection has been proposed since the dawn of STN DBS therapy, based on the idea that the reduced glutamatergic cytotoxicity induced by STN neuromodulation, would favorably affect neurodegeneration.[20] However, the experimental papers supporting this hypothesis were based on the use of artificial animal models that in many ways differ from the degenerative disease affecting patients with PD.[20-22] So far, studies in PD patients have failed to convincingly demonstrate any neuroprotective effect of DBS. For example, a prospective study with serial functional neuroimaging (PET) [23] showed annual progression rates in the caudate and putamen that were within the range of those reported in PD patients without DBS. Furthermore, neuropathology studies showed no differences in the loss of pigmented neurons in the substantia nigra of patients with DBS when compared with PD patients without DBS.[24] There could be several reasons for failure in demonstrating a neuroprotective effect, including the lack of appropriate biomarkers of disease progression and the fact that the few available studies were conducted in patients with advanced PD.

Indeed, DBS has traditionally been offered to PD patients at advanced stages of the disease, when it is possibly too late to halt neurodegeneration because the pathological processes are already too progressed.[25]

An important development is the recent trend toward operating at an earlier stage of the disease.[26] It would be interesting to know whether survival would be more influenced by intervening earlier in the disease course. In this respect, the existing randomized controlled trials (RCTs) comparing the effect of surgery for patients at an earlier stage of the disease with the effect of "best medical treatment"[26] may provide important information after a sufficient follow-up. In this scenario, patients originally allocated to "best medical treatment" could still be offered DBS later in the disease course, allowing detecting a potential effect of a "delayed-onset" of neuromodulation and thus revealing important information on this issue.

In this context, it is important to consider that DBS is a burdensome surgical treatment for the patients with potential serious, albeit rare, complications. More important, especially in the long term, DBS offers little or no benefit for nondopaminergic motor and nonmotor symptoms, affecting cognitive function, independent locomotion, and communication. Notably, these aspects have a predominant influence on quality of life.

Against the background of the relatively small overall differences in life expectancy between PD patients and controls, any true difference in survival between operated and nonoperated patients, if existent at all,

may be very hard to detect. Nevertheless, even if this issue is never fully resolved, it is important to realize that any potentially existent difference in survival is clearly outweighed by a considerable improvement in quality of life that operated patients experience for an extensive period of time. ■

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