

SHORT REPORT

Surgery for Parkinson's disease: lack of reliable clinical trial evidence

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There has been a striking resurgence of interest in surgery for Parkinson's disease (PD) with new targets identified and new procedures developed. This systematic review identified over 500 studies of surgery for PD published since 1990, including over 10 000 patients. However, the authors were unable to assess the value of PD surgery reliably because only seven randomised trials were identified including just 196 patients. Studies of surgery for PD have generally been of poor quality with too few patients, too short follow up, inappropriate choice of outcome measures, and lack of control groups. Much larger, randomised, controlled trials are needed to assess the longer term effects of surgery on patient rated quality of life and cost effectiveness.

The past 10 years have witnessed a resurgence of functional stereotactic neurosurgery for the treatment of advanced Parkinson's disease (PD). This renaissance follows the successful introduction of surgical procedures for PD in the 1950s and their subsequent large scale abandonment with the advent of levodopa and other dopaminergic agents in the 1960s. In the mid-1980s, however, interest was renewed by increasing recognition of the limitations of drug therapy and a better understanding of the pathophysiology of the basal ganglia, coupled with important advances in neuroimaging and improved surgical techniques.

Currently, stereotactic neurosurgical operations for PD are performed at three sites: thalamus, globus pallidus (GP), and subthalamic nucleus (STN) and entail either lesioning or deep brain stimulation (DBS). The aim of ablative procedures and DBS is to reduce or eliminate the abnormal output discharges from the basal ganglia to the cortex and brain stem although the underlying neurodegenerative process remains unmodified; these are therefore symptomatic treatments. Lesioning entails destroying the appropriate target structure using a high frequency electric current. In DBS the target structure is hyperstimulated and thus "turned off" producing a similar result to lesioning.

We provide an evidence based overview of studies involving functional stereotactic neurosurgery for PD that have been conducted over the past decade and reveal important shortcomings in these studies that are important to recognise and respond to.

METHODS

We undertook a systematic review of the published literature in an attempt to assess the efficacy of surgical intervention for PD. This entailed identifying studies of lesioning and DBS for PD published between January 1990 and March 2002; the choice of time period reflected the recent renewed interest in surgical procedures for the treatment of PD. The search did not

include studies of transplantation for PD. We searched databases including the Cochrane Library, Medline, Embase, and PubMed and hand searched major journals in the field as well as conference proceedings to identify presentations made at meetings. Experts in the field were contacted in an attempt to find studies not identified by electronic and hand searching and to identify trials in progress. Research registers were searched to identify ongoing research and additional information was sought from scanning reference lists of retrieved papers, in particular review papers and web sites relating to PD. We also attempted formal meta-analyses of surgical randomised controlled trials (RCTs) that reported the Unified Parkinson's Disease Rating Scale (UPDRS) scale or adverse event data as outcomes, or both.

RESULTS

This systematic review of the published literature identified 503 studies of functional stereotactic surgery for PD. Most of these were small non-randomised, non-controlled studies, and mainly case series. We found 10 700 patients had been included in 496 reported non-randomised studies, averaging about 21 patients per study. Only 2% of studies involved 100 or more patients and only 10% involved 50 or more. There have also been many single case reports. These statistics are based on published reports; the actual number of PD patients that have been included in studies worldwide is likely to be much higher.

We found considerable variation in follow up length across non-randomised studies ranging from days to years. For those studies with reported follow up duration, the maximum follow up period averaged 15 months with only 27% of studies reporting outcome beyond 12 months and only 15% of studies reporting two or more years. Very few studies (1%) followed up patients for five or more years. Moreover, not all patients were followed up for the maximum time period specified in the publications.

Reporting problems were also evident with many studies having poorly defined designs, for example, poorly described eligibility criteria, patient characteristics, follow up duration, and outcome measures. Identifying multiple publications of the same study also caused evaluation problems.

Strikingly, only seven RCTs of stereotactic surgery in PD were identified (table 1). Most were single centre trials and with small numbers of patients (196 patients in total, representing only 1.7% of the total number of patients identified and an average of 30 patients per trial). The maximum follow up in the randomised studies averaged only six months. Two of the randomised studies, including 73 patients,

Abbreviations: PD, Parkinson's disease; GP, globus pallidus; STN, subthalamic nucleus; DBS, deep brain stimulation; RCT, randomised controlled trial; UPDRS, Unified Parkinson's Disease Rating Scale

Table 1 Randomised controlled trials of surgery in Parkinson's disease

| Trial group (main publication) | Intervention | Number of patients randomised | Maximum follow up reported (months) | Main outcome measures reported | Quality of life assessment | Economic assessment |
|---|---|-------------------------------|-------------------------------------|--|----------------------------|---------------------|
| Atlanta Study Group Vittek, <i>et al</i> ¹ | Pallidotomy v medical treatment | 36 | 36 | UPDRS, CAPIT, Schwab and England | No | No |
| Netherlands (Amsterdam) Pallidotomy Study Group (NEPAS) De Bie, <i>et al</i> ² | Pallidotomy v delayed pallidotomy | 37 | 6 | UPDRS, Schwab and England, Dyskinesia Rating Scale, Barthal Index | Yes PDQL | No |
| Argentina Study Group Merello, <i>et al</i> ³ | GP stimulation v Pallidotomy | 13 | 3 | UPDRS, CAPIT, Dyskinesia Rating Scale | No | No |
| Argentina Study Group Merello, <i>et al</i> ⁴ | Bilateral pallidotomy v unilateral pallidotomy + GP stimulation | 6 | 3 | UPDRS, CAPIT | No | No |
| Amsterdam Study Group Schuurman, <i>et al</i> ⁵ | Thalamic stimulation v thalamotomy | 45 | 6 | Dutch Frenchay Activities Index, UPDRS, Essential Tremor Rating Scale, Modified Tremor Scale | Yes Euroqol | No |
| Oregon Study Group Burchiel, <i>et al</i> ⁶ | STN stimulation v GP stimulation | 10 | 30 | UPDRS, Hoehn and Yahr, Dyskinesia Rating Scale | No | No |
| San Francisco Group Marks, <i>et al</i> ⁷ | STN stimulation v GP stimulation | 49 | 6 | UPDRS | Yes SIP | No |

UPDRS, Unified Parkinson's Disease Rating Scale; CAPIT, Core Assessment Programme for Intracerebral Transplantation; PDQL, Parkinson's Disease quality of life questionnaire; SIP, Sickness Impact Profile.

compared PD surgery with medical treatment.^{1,2} Three trials (64 patients) compared electrical stimulation with surgical lesion,^{3,5} and two (59 patients) compared GP with STN stimulation.^{6,7} Attempts to perform meta-analysis of these trials were hampered by a paucity of consistently reported data. For example, standard deviations (SDs), confidence intervals, and p values were often not reported. Some data had to be assumed (for example median = mean; range = SD) or estimated from the available data (for example, using a p value to estimate the SD) and other data were estimated from plots or figures shown. Effect sizes were difficult to calculate because many trials reported percentage change in each arm but did not compare the difference between the two arms. Furthermore, adverse event data were only reported clearly in two RCTs. However, previous estimates of the occurrence of adverse events in surgery for PD indicate that transient adverse events occur in 5%–60% of cases and permanent effects in up to 40%.² In terms of efficacy, results from the surgery compared with medical management RCTs seem to suggest that surgery is superior to medical management in advanced PD patients, at least in the short-term. According to the NEPAS study group, pallidotomy reduces off phase motor impairments by 30% on the UPDRS motor subscale after six months, compared with a 4% worsening in the control arm (difference; $p < 0.001$).² These results are consistent with those of the Atlanta study group: 34% improvement pallidotomy arm and 4% worsening medical arm. Unlike the NEPAS study though, changes over time were not analysed and they gave only statistics for total UPDRS.¹

The RCT comparing unilateral lesion with DBS in the gonal pallidus³ did not show significant differences in the efficacy or safety of the procedures. Similarly, no differences were found between thalamotomy and thalamic stimulation, although stimulation had fewer adverse events.⁵ In the trial investigating simultaneous bilateral pallidotomy versus simultaneous GP lesion combined with contralateral stimulation, the protocol was discontinued because of severe adverse events found in the bilateral pallidotomy arm.⁴ The two trials comparing DBS of the STN and GP demonstrated no significant differences in efficacy between treatment arms and no serious complications of either procedure.^{6,7} The results from the existing RCTs should be interpreted with caution because of the small numbers, short follow up, and possible publication bias. Indeed, many of the surgical RCTs have indicated the need for larger, longer term, and hence more reliable trials.

Most studies of surgery in PD have relied on clinician based rating scales to measure motor impairments and disability, most frequently the UPDRS. Only three trials reported using the Core Assessment Programme for Intracerebral Transplantation.^{1,3,4} Interestingly, only 5% of all studies (including three of the RCTs^{2,5,7}) reported quality of life measures. Only one non-randomised study of surgery for PD reported health economic data.⁸

DISCUSSION

While many of the studies identified in this review suggest that surgery is beneficial for at least some patients in the short-term, the reliable interpretation of these data is severely limited by methodological flaws that are inappropriate for generating unbiased evidence on the long term balance of benefits and risks of surgery for PD. For example, random errors attributable to the play of chance are likely to occur when numbers are small, as with most trials of surgery for PD. Furthermore, non-randomised studies are notoriously unreliable because of the potentially large biases from patient selection factors.⁹ Randomisation avoids selection bias by balancing measurable and unmeasurable prognostic factors between treatment and control groups. There are other potential sources of bias, even in the randomised trials, such as lack of or ineffective blinding, which is usual in PD surgery trials

because of ethical and practical issues surrounding sham surgery¹⁰ but such biases are minor compared with those in non-randomised studies.

Publication bias is important to consider and is likely to exaggerate any real benefits from surgery with successes more likely to be reported than failures. This can be compounded by multiple publications of the same series of patients that are often difficult to identify. Problems in evaluating clinical trial evidence could be minimised by using registration systems to prospectively identify RCTs at initiation. Similarly reporting of trials could be improved by adopting the CONSORT guidelines.¹¹

Ideally, meta-analysis of randomised trials of surgery for PD for each question addressed would help to increase numbers and also give a more balanced view of the total evidence. However, no reliable conclusions about the balance of benefits and risks of surgery could be drawn at this stage because results were too inconsistently and incompletely reported. Such meta-analysis at present would be of limited value because of the inappropriately short follow up in most studies. PD is a progressive disease and it is therefore essential that future studies of surgery evaluate long term effectiveness and safety.

The choice of clinician rated assessments of motor impairments and disability (for example, UPDRS) as sole outcome measures in most previous surgical studies also limits their value. PD in its advanced stages is complicated by additional problems such as depression, dementia, hallucinations, and sleep disturbances. These may have a greater impact on quality of life than physical impairment. It is important that future trials should include reliable, validated, patient rated quality of life measures (for example, PDQ-39) to assess aspects of the patient's life that are considered important by them rather than by clinicians.¹² Furthermore, in this age of limited healthcare resources, cost effectiveness needs to be assessed as well as clinical effectiveness.

To obtain more reliable evidence, there is an urgent need for larger scale randomised trials, with long term follow up, including patient rated quality of life and health economics as outcome measures. Participation in such trials (for example, the UK Medical Research Council's PD SURG Trial) should be encouraged.

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