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Stereotactic pallidotomy in Parkinson's disease

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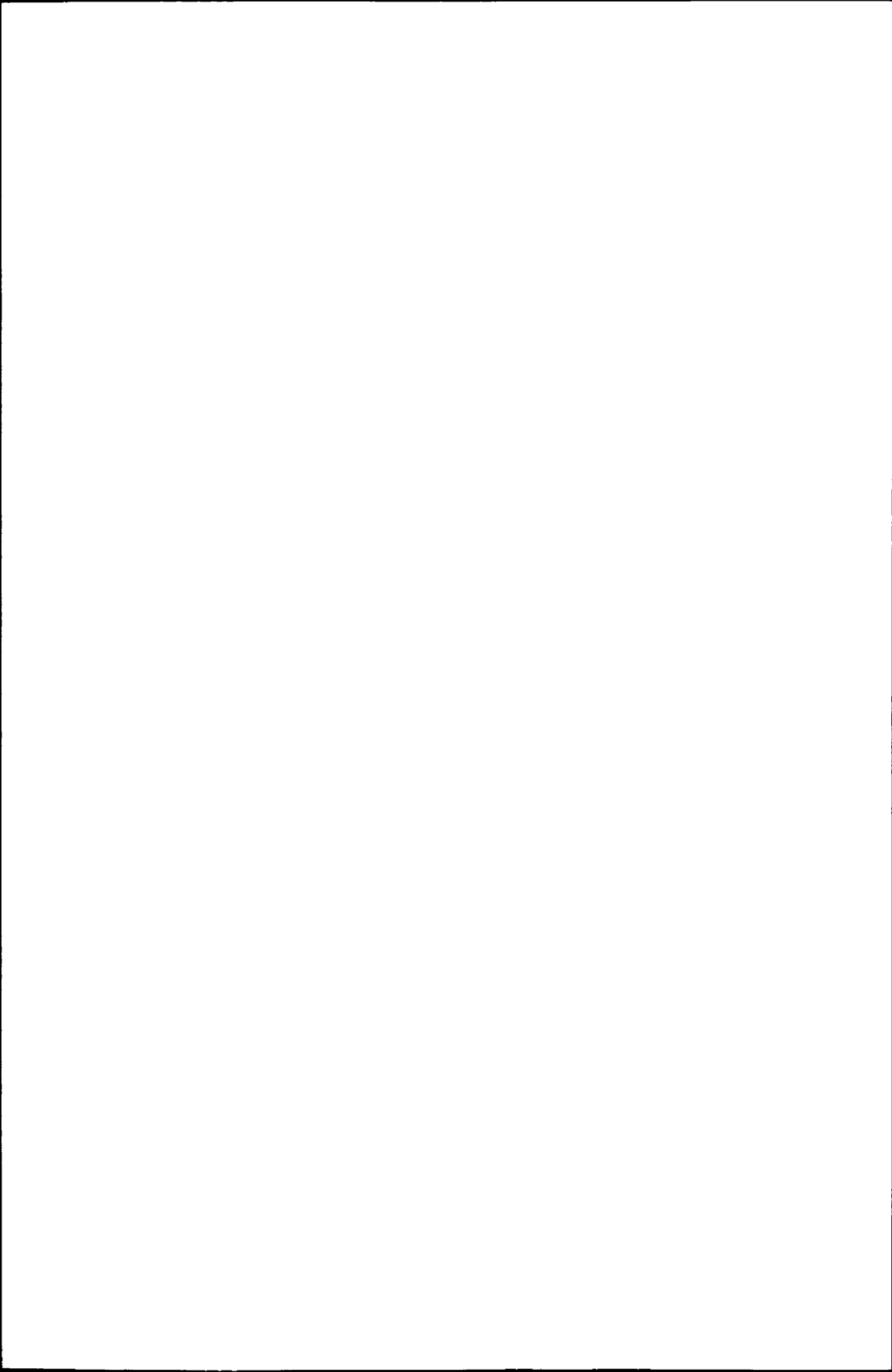
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S u m m a r y



Patients with advanced Parkinson's disease frequently show rapid, seemingly unpredictable, swings between mobility (on phase), usually with dyskinesias, and immobility (off phase). Many of these patients respond unsatisfactorily to adjustments of the pharmacological treatment. Cohort studies suggest that unilateral pallidotomy in patients with advanced Parkinson's disease can improve parkinsonism in the off phase and dyskinesias in the on phase. The main question of this thesis is: do patients with advanced Parkinson's disease benefit from stereotactic pallidotomy?

In **chapter 2** a retrospective study to evaluate the effects of unilateral pallidotomy in patients with advanced Parkinson's disease is presented. Twenty-six patients with Parkinson's disease and disabling dyskinesias, painful or disabling dystonia, or pain as part of Parkinson's disease despite optimal pharmacotherapy underwent a unilateral pallidotomy. In the off phase the median unified Parkinson's disease rating scale (UPDRS) activities of daily living score improved from 26.5 to 20.5 ($p < 0.001$) and the median UPDRS motor examination score improved from 47.5 to 33.0 ($p < 0.001$). In the on phase, the dyskinesias rating scale score was reduced from median 2 to 1 ($p < 0.001$), and the UPDRS activities of daily living and motor examination scores remained unchanged. Thirteen patients had transient, three patients had permanent and two patients had a combination of transient and permanent adverse effects. The transient adverse effects in two patients were classified as major. The results of this study suggest that unilateral pallidotomy may improve symptoms and disability in the off phase and relieves contralateral dyskinesias in the on phase.

In **chapter 3** a randomised, single-blind, multicentre trial is reported, in which we have assessed the efficacy of unilateral pallidotomy in patients with Parkinson's disease. We enrolled 37 patients with advanced Parkinson's disease who had, despite optimal pharmacological treatment, at least one of the following symptoms: severe response fluctuations, dyskinesias, painful dystonias, or bradykinesia. Patients were randomly assigned to unilateral pallidotomy within 1 month or to pallidotomy after the primary outcome assessment, 6 months later. The primary outcome was the difference between the groups in median changes on the motor examination section of the UPDRS score done in the off phase. Secondary outcome measures included levodopa-induced dyskinesias (dyskinesia rating scale) and extent of disability. The median UPDRS motor examination off phase score of the pallidotomy patients improved from 47 to 32.5, whereas that of control patients slightly worsened from 52.5 to 56.5 ($p < 0.001$). In the on phase the median dyskinesia rating scale score improved 50 percent in pallidotomy patients compared to no change in controls ($p = 0.02$). The UPDRS activities of daily living off phase score improved with a median of 7 in the pallidotomy group ($p = 0.002$, compared to controls). Two treated patients had major adverse effects. We concluded that unilateral pallidotomy is an effective

treatment in patients with advanced Parkinson's disease, who have an unsatisfactory response to pharmacological treatment.

In the same trial, we investigated whether unilateral pallidotomy affects cognitive and behavioural functioning, which is reported in **chapter 4**. At baseline and after 6 months, we assessed neuropsychological functioning. We performed neuropsychological tests of language, visuospatial function, memory, attention, and executive functions. Self ratings and proxy ratings of memory problems and dysexecutive symptoms were also collected. No significant differences over time were found between pallidotomy and control groups, with the exception of a decrease of verbal fluency in the left-sided pallidotomy group. The study suggests that unilateral pallidotomy is relatively safe with respect to cognition and behaviour.

In **chapter 5** the follow-up study of the trial mentioned above is reported. The aims of this study were to: (1) assess clinical outcome; (2) report the adverse effects; (3) study cognitive and behavioural effects; (4) investigate the relationship between lesion location and outcome; and (5) investigate possible preoperative patient characteristics predictive for good outcome. Of the 37 patients enrolled, 32 had a unilateral pallidotomy. Multivariate logistic regression was used to identify preoperative patient characteristics independently associated with good outcome. Off phase assessment showed a reduction in parkinsonism from 49 to 36.5 points on the motor section of the UPDRS 6 months after surgery ($p < 0.001$). Improvements were also demonstrated for activities of daily living ($p < 0.001$) and quality of life ($p < 0.001$). In the on phase dyskinesias were reduced ($p < 0.001$). All effects lasted up to 12 months after surgery. Three patients suffered major permanent adverse effects. Besides worsening of verbal fluency following left-sided surgery, systematic cognitive deterioration was not detected. We were not able to discern an association between lesion location and outcome. Patients taking less than 1000 levodopa equivalent units (LEU) per day were more likely to improve (adjusted odds ratio 9.1, 95 percent confidence interval [CI] 1.2-70.8). We concluded that the positive effects of unilateral pallidotomy are stable up to one year after surgery and that patients taking less than 1000 LEU per day are more likely to improve.

In **Chapter 6** we report a retrospective study, which we did to evaluate the effects of bilateral pallidotomy in patients with advanced Parkinson's disease. Thirteen consecutive patients with Parkinson's disease had a staged bilateral pallidotomy. The median off phase UPDRS motor examination score was reduced from 43.5 to 29 points ($n=8$, $p=0.025$) after the first pallidotomy and it was further reduced to 23.5 points after the second pallidotomy (not statistically significant [NS]). The UPDRS activities of daily living off phase score improved from 28.5 to 20.5 points after the first pallidotomy and was 19 after the second pallidotomy ($n=6$, NS). The Schwab and England scale off phase score showed

an improvement after both procedures, first from 40 to 60 ($n=8$, $p=0.048$), and thereafter to 90 ($p=0.026$). On phase dyskinesias were reduced substantially. Ten of 13 patients had adverse effects of which five had problems with speech. One patient became hemiplegic due to a delayed infarction. We concluded that bilateral pallidotomy reduces dyskinesias. A second contralateral pallidotomy may reduce parkinsonism, although to a lesser degree compared to the first pallidotomy and with an increased risk for adverse effects.

We did a systematic review to study the frequency of morbidity and mortality of stereotactic pallidotomy, which is reported in **chapter 7a**. The MEDLINE electronic database was searched for articles published between January 1992 and December 2000 using the key word 'pallidotomy'. Studies were selected according to the following criteria: reporting of clinical data, reporting of original data, unequivocal description of morbidity and mortality, and reporting of unselected consecutive cases. For unilateral pallidotomy, 12 prospective studies were included containing 334 patients. Of these patients, 30.2 percent (CI 25.3-35.2) had adverse effects and 13.8 percent (CI 10.1-17.5) had permanent adverse effects. A symptomatic infarction or haemorrhage occurred in 3.9 percent (CI 2.1-6.6). Mortality was 0.9 percent (CI 0.2-2.6). The most frequent adverse effects were problems with speech (11.1 percent) and facial paresis (8.4 percent). For bilateral pallidotomy, five historical cohort studies were eligible, containing 20 patients. Fourteen patients had an adverse effect and most frequent were impairments of speech and cognition.

In **chapter 7b**, we report on transient hiccups after pallidotomy for Parkinson's disease, which we saw in seven patients. The hiccups started immediately after the operation or the next day, were intermittent and the bouts of hiccup of six patients resolved within 3 days after the procedure. One patient complained of yawning more often and frequent bouts of hiccup for 6 months. Based on our experience we hypothesise that the globus pallidus or a neighbouring structure may be involved in a supramedullary system involved in triggering hiccups.

In **chapter 8** we conclude that unilateral pallidotomy is an effective treatment in patients with advanced Parkinson's disease, who respond unsatisfactorily to pharmacological treatment. Bilateral pallidotomy reduces parkinsonism and dyskinesias, but its effectiveness is limited by the high complication rate. An important question is the place of pallidotomy in advanced Parkinson's disease in view of the results of cohort studies that investigated the effects of deep brain stimulation in the subthalamic nucleus. The results of studies comparing both procedures have to be awaited.

