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Chapter **7a**

Morbidity and mortality following pallidotomy in Parkinson's disease: a systematic review

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Summary

Objective To study the frequency of morbidity

and mortality of pallidotomy.

Methods We searched the MEDLINE electronic database for 'pallidotomy' articles published between January 1992 and December 2000. We selected studies by the following criteria: original clinical data, unequivocal description of morbidity and mortality, and unselected consecutive cases. We extracted: number of patients, unilateral or bilateral procedures, age, localisation technique, follow-up time, number of patients with adverse effects, number of patients with permanent adverse effects (> 3 months), types of adverse effects, and mortality.

Results For unilateral pallidotomy, 12 prospective studies contained 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 frequency of adverse effects was 14.4 percent (CI 4.7-24.1) higher and the frequency of stroke was 4.9 percent (CI 1.4-8.4) higher in the series with microelectrode recording. 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.

Conclusions Unilateral pallidotomy has a risk of 14 percent for permanent adverse effects. A symptomatic infarction or haemorrhage occurs in 4 percent of patients and mortality is 0.9 percent.

Introduction

After the reintroduction of pallidotomy as a treatment for Parkinson's disease in 1992 many studies have been published on the efficacy of the procedure.² The most consistent effect of pallidotomy is the reduction of contralateral levodopa-induced dyskinesias and dystonia. In addition, symptoms like contralateral tremor, hypokinesia and rigidity are reduced.^{3,5}

In recent years, stereotactic techniques have changed, mainly due to advances in neuroimaging and the increasing use of physiological intraoperative localisation techniques. The studies concerning efficacy of pallidotomy and widely accepted outcome measures are small and most are uncontrolled. Adverse effects and mortality have been reported in varying frequencies.^{4,6} We systematically review the frequency of morbidity and mortality of unilateral and bilateral pallidotomy.

Methods

Literature search We searched the MEDLINE electronic database for English articles published between January 1992 and December 2000 using the key word 'pallidotomy'. The reference lists of the relevant articles were scanned for additional studies.

Study selection We selected studies according to the following criteria: (1) reporting of clinical data in Parkinson's disease (no radiological procedures or technical notes), (2) reporting of original data (no reviews or editorial notes), (3) unequivocal description of morbidity and mortality, (4) and reporting of unselected consecutive cases (no case reports). For studies with overlapping data sets, we choose the one with the largest population. In case of a dual publication, the study was used only once.

If it was clearly stated or deducible from the article that the described study was prospective, it was labeled as such. The other studies were regarded as historical cohort studies. The latter set included reports in which was not clearly stated whether or not there was a study protocol prior to the actual pallidotomies, irrespective of the use of the core assessment program for intracerebral transplantations protocol (CAPIT).⁷

Data extraction Two investigators (RMAdB and JDS) independently reviewed all reports. A standard checklist was used to assess eligibility and to extract the following data: number of patients, unilateral or bilateral procedures, age, localisation technique (MRI or CT, ventriculography, microelectrode recording, and microelectrode or macroelectrode stimulation), follow-up time, number of patients with adverse effects, number of patients with permanent adverse effects (>3 months), types of adverse effects, and mortality. Weight increase was not regarded an adverse effect. Results were compared and discrepancies were resolved in a meeting.

Analysis We summed the data from the different studies and calculated the 95 percent confidence interval (CI) to assess overall accuracy. Differences in frequencies are expressed in CIs.

Results

Of the 328 publications yielded by the literature search, 301 were excluded for the following reasons: not reporting clinical data concerning pallidotomy in Parkinson's disease (83), no original data (70), no unequivocal description of morbidity and mortality (119), reporting of selected or non consecutive cases (seven), and double publication (22).

Unilateral pallidotomy For unilateral pallidotomy, 23 studies were included; 12 were considered prospective and 11 historical cohort studies. The prospective studies incorporated 334 patients (table 1). One hundred and one patients (CI 25.2-35.2 percent) experienced at least one adverse effect and 46 patients (CI 10.1-17.5 percent) had permanent adverse effects. A symptomatic infarction or

Table 1. The frequency of patients with adverse effects from unilateral pallidotomy; prospective studies

Reference number	Number of patients	Mean age	Micro-electrode recording	Mean follow-up time in months	Number of patients with adverse effects (percentage)	Number of patients with permanent adverse effects (percentage)	Number of patients with infarction or hemorrhage (percentage)	Number of patients that died (percentage)
18	33	60.3	Yes	12	1 (3.0)	0	0	0
19	22	63.8	No	9.5	6 (27.3)	4 (18.2)	0	0
20	24	61	No	8.1	6 (25.0)	3 (12.5)	1(4.2)†	1 (4.2)
21	29	Not stated	Yes	3	4 (13.8)	0	0	0
3	44	58.8	Yes	13.5	27 (61.4)	14 (31.8)	2 (4.5)	0
22	36	65	Yes	5.3	5 (13.9)	2 (5.6)	0	0
4	26	55.9	Yes	6.1	17 (65.4)	7 (26.9)	5 (19.2)	2 (7.7)
6	26	59.3	Yes	5.2	16 (61.5)	9 (34.6)	4 (15.4)	1 (3.8)
5	19	60.6	No	6	9 (47.4)	6 (31.6)	0	0
23	58	67	No	9	5 (8.6)	1 (1.7)	0	0
24	10	56.1	Yes	12	2 (20.0)	0	0	0
13	7	59	Yes	3	3 (42.9)	0	1 (14.3)	0
Total	334				101	46	13	4
Perc					30.2	13.8	3.9	1.2
CI					25.3-35.2	10.1-17.5	2.1-6.6	0.3-3.0

† Haemorrhage 2 weeks after pallidotomy, patient died 2 days later; Perc=percentage; CI= 95% confidence interval.

haemorrhage occurred in 13 patients (CI 2.1-6.6 percent). Four patients (CI 0.3-3.0 percent) died following unilateral pallidotomy; two following a deep haemorrhage, one with a massive hemorrhagic infarction, and one suffered an intracerebral haemorrhage 2 weeks after surgery. In the studies with microelectrode recording, the frequency of adverse effects was 14.4 percent (CI 4.7-24.1) higher and the frequency of infarction or haemorrhage was 4.9 percent (CI 1.4-8.4) higher. In eight studies adverse effects were defined as major or minor.^{3-6,13,18,21,23} Of these 242 patients, 15 patients (CI 3.5-10.0 percent) experienced major permanent adverse effects, including the three patients that died, and 22 patients (CI 5.8-13.4 percent) experienced minor permanent adverse effects.

The historical cohort studies incorporated 359 patients (table 2). At least one adverse effect was experienced by 73 patients (CI 16.2-24.5 percent) and permanent adverse effects by 23 (CI 4.1-9.5 percent). Seven patients (CI 0.8-4.0 percent) had a symptomatic infarction or haemorrhage and one patient died. There was no difference in frequency of adverse effects and mortality between series with or without microelectrode recording.

Table 2. The frequency of patients with adverse effects of unilateral pallidotomy; historical cohort studies.

Reference number	Number of patients	Mean age	Micro-electrode recording	Mean follow-up time in months	Number of patients with adverse effects (percentage)	Number of patients with permanent adverse effects (percentage)	Number of patients with infarction or hemorrhage (percentage)	Number of patients that died (percentage)
25	55	58	No	7.5	4 (7.3)	1 (1.8)	3 (5.5)	0
26	6	Not stated	No	1	2 (33.3)	1 (16.7)	0	1 (16.7)
27	20	65.5	Yes	3	4 (20.0)	0	0	0
28*	12	56	No	3.5	1 (8.3)	1 (8.3)	0	0
29	26	55.8	No	5 (median)	18 (69.2)	5 (19.2)	0	0
30*	20	65.3	Yes	8.4	8 (40.0)	7 (35.0)	0	0
31	42	60.6	Yes	7.6	8 (19.0)	0	0†	0
32	23	58.2	Yes	3	6 (26.1)	0	1 (4.3)	0
33	75	61	No	Not stated	12 (16.0)	5 (6.7)	1 (1.3)†	0
34	36	64.1	Yes	11	6 (16.7)	3 (8.3)	2 (5.6)	0
35	44	67.4	Yes	8.7	4 (9.1)	0	0	0
Total	359				73	23	7	1
Perc					20.3	6.4	2	0.3
CI					16.2-24.5	4.1-9.5	0.8-4.0	0.0-1.5

* Excluding weight gain; † in each study, two patients with a silent cortical haemorrhage are not included; Perc=percentage; CI= 95% confidence interval.

The proportion of patients with at least one adverse effect was 9.9 percent (CI 3.5-16.4) higher and the proportion of permanent adverse effects was 7.4 percent (CI 2.9-11.8) higher in the prospective series compared to the historical cohort series. Table 3 shows the types of adverse effects. Of the 334 patients in the prospective series 37 (11.1 percent) experienced problems with speech, which was permanently affected in 20 patients (6.0 percent) including anarthria (one), dysarthria (12), hypophonia (four), and dysphasia (three). Seventeen patients suffered from dysphagia, which was permanent in eight and 13 patients had acute confusion or somnolence following unilateral pallidotomy.

Table 3. Adverse effects of unilateral pallidotomy in the prospective studies (334 patients)

Adverse effect	Transient adverse effects (number of patients)	Permanent adverse effects (number of patients)
Infarction		3
Superficial hemorrhage	1	4
Deep hemorrhage		5
Acute confusion or somnolence	13	
Anarthria		1
Contralateral neglect		2
Changes in personality or behavior*	6	13
Deep venous thrombosis	1	
Depressive episode	2	
Dysarthria	15	12
Dysphagia	9	8
Dysphasia	1	3
Facial paresis	20	8
Hemiparesis	7	1
Hiccups	1	
Hypersalivation		7
Hypophonia	1	4
Pneumonia	2	
Postural instability	2	4
Pseudobulbar syndrome	1	
Psychosis	2	3
Seizure	1	1
Urinary incontinence	1	1
Visual field defect		8
Worsening of dementia		1
Worsening of handwriting	6	4

Some patients had more than one adverse effect; * Other than psychosis.

Bilateral pallidotomy For bilateral pallidotomy, five studies were eligible, which were all historical cohort studies (table 4). These studies included 20 patients. Fourteen patients had an adverse effect. There were no patients with a stroke and there was no mortality. Five patients had problems with speech, four patients suffered from cognitive decline, three patients had a visual field defect, and three a depression.

Table 4. The frequency of patients with adverse effects of bilateral pallidotomy

Reference number	Number of patients	Mean age	Staged or simultaneous bilateral pallidotomy	Microelectrode recording	Mean follow-up time in months	Number of patients with adverse effects (percentage)	Number of patients with permanent adverse effects (percentage)
36	2	64.5	Staged	No	Not stated	2	2
37	2	51	Staged	No	9	1	1
28	8	60.6	Simultaneous	No	3-4	5	5
38	4	62.3	Simultaneous	No	Not stated	4	2
39	4	Not stated	Staged	Yes	Not stated	2	2
Total	20					14	12
Perc						70	60
CI						45.7-88.1	36.1-80.9

Perc=percentage; CI= 95% confidence interval.

Discussion

Our study showed that approximately 30 percent of patients experienced an adverse effect after unilateral pallidotomy, which was permanent in about 14 percent of patients in the prospective studies. A symptomatic infarction or haemorrhage occurred in almost four percent of the patients and mortality was one percent. These numbers are in agreement with other stereotactic neurosurgical procedures; for example, the rate of permanent complications of stereotactic thalamotomy ranges from nine to 47 percent,⁸⁻¹⁰ and the rate of intracerebral haemorrhage in general stereotactic neurosurgery from one to four percent.^{11,12} Although these numbers are high, most authors of the included reports conclude that improvements outweigh adverse effects. We only found five historical cohort studies on bilateral pallidotomy unequivocally reporting adverse effects. Numerous articles reported both on unilateral and bilateral procedures without differentiating the adverse effects and without stating clearly which patients underwent unilateral and which patients underwent bilateral procedures. Because we only found 20 patients who had undergone bilateral pallidotomy, the outcome—adverse effects in 70 percent of the patients—has to be interpreted with major reservations.

Randomised trials would provide the most accurate information on adverse effects and their frequencies. However, only three small randomised trials were done and one of them was published as an abstract only.^{5,13,14} These trials alone cannot provide sufficient information regarding adverse effects and their frequencies,

certainly not for the less frequent adverse effects, simply because of the large number of patients required. For that reason, we performed a systematic review of trials and consecutive cohort studies.

We divided the studies in two sets. One set included studies which were prospective in design. The other set consisted of historical cohort studies. The latter set included reports in which was not clearly stated whether or not there was a study protocol before the pallidotomies took place. We found that the proportion of patients with at least one adverse effect was almost ten percent higher in the prospective series compared to the historical cohort series. The number of patients with permanent adverse effects was eight percent higher in the prospective series. These findings are consistent with the hypothesis that surgical studies with prospective collection of data report considerably higher rates of adverse effects than retrospective studies.^{15,16}

Only studies published after 1992 were included, because in that year pallidotomy was reintroduced¹ and by that time the stereotactic functional neurosurgical procedure had been modernised, which could affect morbidity and mortality.

One of the main controversies in stereotactic functional neurosurgery concerns the use of microelectrode recording for target localisation. The main arguments in favor of microelectrode recording have been: improved accuracy of lesion or deep brain stimulation electrode placement, decreased lesion size, and a decrease of adverse effects, which altogether would bring about better results of surgery.¹⁷

We found that with microelectrode recording for pallidotomy the frequency of adverse effects was 14 percent higher and the frequency of stroke was five percent higher. It could be that groups using microelectrode recording are more reliable in reporting their results, another reason could be that these groups are more likely to report on their first pallidotomies, or that microelectrode recording involves more electrode passes for target localisation. However, regarding the nature of the data, we cannot address with certainty the relative benefits or adverse effects related to the use of microelectrode recording. The results of randomised trials investigating the risks and benefits of microelectrode recording have to be awaited.

Until now, stereotactic functional neurosurgery has been reserved for patients in an advanced stage of the disease with an unsatisfactory response to adjustments of pharmacological treatment. Because of the risks on adverse effects and mortality, we find it undesirable to perform unilateral pallidotomy in patients with less severe disease. On the other hand, functioning in activities of daily living has to be reasonably well in the on phase, since patients will probably not improve beyond this level.⁵

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