Risks of intracranial hemorrhage in patients with Parkinson's disease receiving deep brain stimulation and ablation


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Abstract

Objective: This study analyzed risk factors for hemorrhage in a large series of deep brain stimulation (DBS) and ablation procedures in patients with advanced Parkinson’s disease (PD).

Methods: Six hundred and forty four subjects with advanced PD treated with DBS or ablation procedures between March 1999 and December 2007 were enrolled in the study. Procedures were performed by the same surgeon, and included DBS in 126 patients, ablation in 507 patients and DBS after prior unilateral ablation procedures in 11 patients. Of 796 target procedures, 207 were DBS including 202 subthalamic nucleus (STN) targets, 3 ventralis intermedius nucleus (Vim) targets and 2 globus pallidus internus (GPI) targets, and the others were 589 ablation procedures including 474 GPI targets and 115 Vim targets. Postoperative CT or MRI was performed in all patients within 24 h of lead implantation or ablation treatment. Statistical correlation analysis of risk factors for intracranial hemorrhage (ICH) was performed by stepwise logistic regression. Explanatory variables were patient age, sex, blood pressure, anatomical targets, the number of microelectrode recording (MER) penetrations and surgical modality.

Results: Postoperative symptomatic ICH occurred in 10 cases (8 pallidotomy and 2 thalamotomy) and asymptomatic ICH in 14 cases (9 pallidotomy, 4 thalamotomy and 1 DBS). Hypertension and surgical modality were significant factors contributing to hemorrhage (both \( P < 0.05 \)). The likelihood of hemorrhage in hypertensive patients was 2.5 times that in normotensive patients. The risk of hemorrhage during ablation was 5.4 times that in DBS. The number of MER trajectories did not significantly correlate with ICH occurrence \( (P = 0.07) \). No statistically significant difference was found in age, sex and anatomical targets.

Conclusion: This study demonstrated that hypertension is a risk factor for ICH in PD patients. DBS is generally a safe surgical modality as compared with ablation. Increasing microelectrode trajectories seemed to increase the risk of ICH, but no statistically significant difference was found \( (P = 0.07) \).

1. Introduction

Since Laitinen et al. [1] reported posteroventral pallidotomy (PVP) for alleviating severe symptoms of Parkinson’s disease (PD) in 1992, it has been generally accepted as an accepted ablation procedure for the treatment of PD [2,3]. But in recent years, PVP is being replaced gradually by deep brain stimulation (DBS) because there is increasing clinical evidence that the latter is safer and more effective [4–6].

Current studies mainly focus on the therapeutic effects, postoperative morbidity and side effects of DBS and ablation in PD treatment. Intracranial hemorrhage (ICH) is a severe complication associated with both PVP and DBS [7–13]. A series of publications on ICH in DBS or PVP have highlighted hypertension as a risk factor for ICH [10,12,14]. However, correlations between microelectrode recording (MER) and ICH remain unclear [8,10,12]. To obtain clinical evidence for different applications of MER to the same series of study and explore possible correlations between ICH and multiple surgical modalities including ablation and DBS, the present study was designed to see whether patient age, sex, blood pressure, anatomical targets, the number of MER penetrations and surgical modality constitute risk factors for ICH by logistic regression analysis.

* The review of this paper was entirely handled by an Associate Editor, En-King Tan.
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Abbreviations: CRW, Cosman-Robert-Wells; CT, computed tomography; DBS, deep brain stimulation; HFC, Fred Haer Corporation; CP, globus pallidus; GP, globus pallidus internus; ICH, intracranial hemorrhage; IPC, interal pulse generator; MER, microelectrode recording; MRI, magnetic resonance imaging; PD, Parkinson’s disease; PVP, posteroventral pallidotomy; STN, subthalamic nucleus; Vim, ventralis intermedius nucleus.
2. Clinical subjects and methods

2.1. Patients

Included in the present study were 644 patients (379 male and 265 female) with medically refractory PD who received surgical treatment in Shanghai Changhai Hospital between March 1999 and December 2007. They ranged in age from 42 to 80 years with a mean of 64.7 ± 8.3 years. The mean course of PD was 5.7 ± 2.0 years (range 3–19 years). 46 patients who took aspirin or other anticoagulants stopped the medication one week prior to surgery, and 109 patients who had hypertension on admission were monitored and their hypertension brought under control prior to surgery. Coagulation function and platelet count of all 644 patients were normal.

Of the 644 PD patients, 507 patients underwent ablation mostly between 1999 and 2001, and 126 patients underwent DBS mainly between 2002 and 2007. The remaining 11 patients had undergone ablation on one side of the brain prior to this study and DBS on the other side during the study period (Table 1).

Some of the patients who received bilateral surgical intervention, pallidotomy was performed on one side and thalamotomy on the other side depending on the clinical condition of the individual patients: We did this to minimize side effects possibly arising from bilateral intervention of the same target. As some patients received treatment in multiple locations, the number of cases was inconsistent with the number of targets. The number of DBS targets was 207 including subthalamic nucleus (STN) (n = 202), ventralis intermedius nucleus (Vim) (n = 3) and globus pallidus internus (GPi) (n = 2). The number of ablation targets was 589 including GPi (n = 474) and Vim (n = 115) (Table 1). All the procedures were approved by the Academic Board of the Second Medical Military University (Shanghai, China). DID THE PATIENTS SIGN INFORMED CONSENT?

2.2. Surgical procedures

Under local infiltrative anesthesia subjects were placed in a Cosman-Robert-Wells (CRW) frame that was oriented parallel to the infraorbitalmeatal line. The target was located by 1.5 Tesla MRI (Siemens, Erlangen, Germany). The targeting images were 2 mm thick. No-overlap slices were obtained in axial, sagittal and coronal planes. The tentative target coordinates were based on the anterior commissure-posterior commissure line and direct visualization of MRL.

After induction of local anesthesia, a hole was drilled over the coronal suture and the dura was opened adequately for direct cortical exposure. MER (Fred Haer Corporation) was performed in all cases targeting GPi, and some of the cases targeting Vim or STN. The number of microelectrode recordings was dictated by the quality of the MER. If the signal was typical, one or two trajectories were recorded, and if the signal was atypical, 3–4 trajectories were recorded. Multiple trajectories were inserted separately for MER during operation. Previously we used to record several trajectories. More recently as the result of accumulated experience only one trajectory is usually recorded. The guide tube for the microelectrode was terminated at 35 ± 40 mm superior to the stereotactic target. The microelectrode was advanced with an electronic micro-driver. Recording was made from a point 20 mm above the presumptive target. Micro-stimulation through the electrode was applied to estimate the distance from the internal capsule or the optic tract to ensure a safe placement of DBS electrode or lesions.

For DBS, a quadripolar lead (Medtronic Model 3387 for GPi, and Model 3389 for STN and Vim) was used to conduct the stimulation. A guide tube for the DBS lead with a blunt tip styllet was then introduced into the brain parenchyma to a point 10 mm proximal to the target. Test stimulation was performed to record voltage thresholds for stimulation and adverse effects.

The DBS electrode was anchored to the burr-hole ring (a plastic ring designed to fit the 14 mm burr hole) by wedging the electrode into one of its two grooves. An additional plastic burr-hole cap further locked the DBS lead into the burr-hole ring. In 87 patients who did not undergo MER, the target position was confirmed by intraoperative MRI scan with CRW stereotactic frame. The actual target was modified in 21 cases in subsequent procedures; 19 of which were adjusted by 2.0–3.5 mm in depth, and the remaining 2 cases were adjusted by 1.5–2.0 mm on the x and y coordinates.

For those patients for whom the therapeutic effect was satisfactory at a low voltage (<3.5 V) without causing significant side effects and in the absence of complications such as ICH, an internal pulse generator (IPG, Itrel or Soletra, Medtronic) was placed in the infraclavicular fossa subcutaneously under general anesthesia. In the remaining patients with major motor symptoms involving posture, balance or gait who failed to demonstrate adequate therapeutic efficacy intraoperatively, a temporary pulse generator was used for 4–14 days until the symptoms improved, whereupon an IPG was implanted.

Macroelectrode stimulation was conducted for ablation by using a macroelectrode with 11-mm diameter and a 2 mm exposed tip (Radionics, Burlington, MA). Radiofrequency lesions were created by applying 80 °C for 60 s. Three lesions were made at 2 mm intervals in one (for thalamotomy) or two trajectories (for pallidotomy) of the electrode to produce an oval lesion.

A postoperative MRI or CT scan was performed in all patients within 24 h of the lead implantation or the ablation procedure. Hemorrhage was scored as symptomatic (associated with any new neurological deficit lasting for longer than 24 h) or asymptomatic. Subjects with symptomatic hemorrhage were followed for at least one year to evaluate the ultimate neurological outcome [8].

2.3. Statistical analysis

Risk factors for ICH were studied in patients receiving different treatments by using logistic regression analysis. The dependent variable was hemorrhage, which in particular was classified into two categories: hemorrhage and no hemorrhage. Explanatory variables included age (comparing the effect of being one year older), sex (male vs. female patients), hypertension (hypertensive vs. normotensive patients), anatomical target (GPi vs. Vim vs. STN), MER (the number of MER penetrations) and surgical modality (ablation vs. DBS). The purpose of this analysis was to determine risk factors contributing to hemorrhage with respect to sex, age, blood pressure, anatomical targets, MER and surgical modality.

3. Results

Of the 644 patients, 10 (8 pallidotomy and 2 thalamotomy) developed postoperative symptoms of ICH, including hemorrhage in the trajectory tracks in 4 patients and the target areas in 6 patients (Fig. 1). The intra-operative symptomatic hemorrhage cerebrovascular rate was 1.70% (10/589 procedures). There was no symptomatic cerebral hemorrhage as a result of DBS.

Of the 10 patients with symptomatic hemorrhage, surgery was terminated immediately in 3 because aphasia and hemiplegia developed during thromcoagulation. Postoperative emergency CT scan indicated that a hematoma had formed in the target area. Hemorrhagic symptoms were noted within 1–3 days post surgery in 3 cases, where CT examination revealed that the hemorrhage involved the cerebral ventricle in 2 cases, and the target area in the other. In another case, a small hematoma in the trajectory track expanded 6 days post surgery, causing hemiplegia and disturbance of consciousness. In one of the remaining 3 cases, hematoma occurred in the trajectory track and then broke into the cerebral ventricle, and in the other 2 cases hematoma was found in the target area following discharge from hospital by emergency CT examination when the patients became unconscious and hemiplegic.

Of the 10 symptomatic patients, 6 patients underwent emergency surgery under general anesthesia, including evacuation of the intracranial hematoma and decompression by removing the bone flap in 4 patients. In 2 cases the trajectory hematoma was removed by expanding the bone hole. The long-term sequelae included mild hemiplegia in 2 cases, hemiplegia plus aphasia in one case, and hemiplegia plus coma in 3 cases. The remaining 4 patients whose hematoma volume was less than 30 ml were treated conservatively, of whom 2 patients recovered well, and the other 2 patients remained hemiplegic and aphasic. No deaths occurred during the course of surgical treatment.

Asymptomatic ICH was identified in 14 patients (9 pallidotomy, 4 thalamotomy and 1 DBS) by CT and MRI, in the trajectory track in 6 patients and in the target site in the remaining 8 patients, all of them treated conservatively. The hematoma volume was monitored and their hemorrhage brought under control prior to surgery. 8 patients showed clinical improvements, 4 patients showed no visible changes and 2 patients showed further deterioration.
whom presented with no obvious clinical symptoms, and whose hematomas were absorbed spontaneously after conservative treatment. The overall asymptomatic cerebral hemorrhage rate was 2.21% (13/589 procedures), and 0.48% (1/207 procedures) in DBS.

The results in Table 2 indicate that hypertension and surgical modality were significant factors contributing to hemorrhage ($P < 0.05$). The odds ratio of hypertension, MER and surgical modality was greater than 1. The variable with the largest statistically significant odds ratio was surgical modality. The risk of ablation causing hemorrhage was 5.4 times that of DBS. Hypertension was one further important variable with the odds ratio of 2.455, indicating that hypertensive patients were 2.5 times more likely to develop hemorrhage than normotensive patients. Although no significant correlation was found between MER trajectory and ICH occurrence ($P = 0.07$), increasing microelectrode trajectories trended to increase the risk of ICH. No statistically significant difference was found in age, sex and anatomical target.

4. Discussion

4.1. ICH occurrence

Intracranial hemorrhage is a serious complication of stereotactic surgery including DBS and ablation in the treatment of PD. ICH occurrence in the present series of ablation surgery was 3.90% (23/589 procedures), including 1.70% (10/589 procedures) symptomatic cerebral hemorrhage and 2.21% (13/589 procedures) asymptomatic cerebral hemorrhage. ICH occurrence in DBS was 0.48% (1/207 procedures), including only one case of asymptomatic cerebral hemorrhage. ICH occurrence reported in the literature varies with different studies [7–13,15–23].

A meta-analysis by Terao et al. [13] including 22 studies of MER-guided stereotactic operation for movement disorders from 1995 to 2002 showed that the incidence of ICH was 2.9%. However, the incidence in Terao’s own study was 9.5% (11/116), where ICH occurred in 9 (15.8%) of 57 coagulation operation cases, and intraventricular hemorrhage occurred in 2 (3.4%) of 59 DBS cases. Binder et al. [8] reported that the asymptomatic ICH rate was 2.1% and the symptomatic ICH rate was 1.2% in patients receiving DBS.

4.2. Causes and types of ICH

In the present study, ICH was classified by the site of hemorrhage: trajectory track and target area. Hemorrhage in the trajectory of ablation was 1.53% (9/589 procedures), which could be attributed to tissue penetration by the guide tubes for the microelectrodes, the tip of the microelectrode and the radiofrequency electrode probe. As the guide tubes for FHC microelectrodes are relatively thick, we therefore suppose that the guide cannula probe is more likely to cause hemorrhage than the radiofrequency electrode probe. Ben-Haim et al. [16] reported that a new microelectrode with a smaller diameter to minimize the volume of brain parenchyma penetrated during microelectrode recording leads to decreased rates of hemorrhage, particularly in the ventricles.

Hemorrhage in the target area was 2.38% (14/589 procedures) in ablation patients of the present study. Although radiofrequency thermocoagulation and penetration of the microelectrode and radiofrequency electrode probe may both cause hemorrhage in the target area, we think that radiofrequency thermocoagulation is the most likely cause, because the 2–5 mm asymptomatic hemorrhage in our series was exactly in the target area. In addition, hemiplegia and disturbance of consciousness occurred in 3 cases of symptomatic ICH in the target area during the thermocoagulation, suggesting that radiofrequency thermocoagulation is the most significant risk factor of ICH [13,18], possibly due to adhesion of the electrodes to the brain tissue. Methods to minimize the risk include lowering temperature and reducing time duration of thermocoagulation, embrocating the electrode tip with paraffin oil prior to operation, replacing the radiofrequency electrode regularly and limiting the size of the final lesion [18]. It is notable that there were 3 cases of delayed intracerebral hematoma in our study, among which 2 cases occurred 1–2 days after discharge, possibly implying that there was a correlation between ICH and physical activity, emotional excitation and uncontrolled hypertension.

4.3. Risk factors contributing to ICH

Apart from surgical modalities, risk factors contributing to ICH in PD procedures include age, sex, and blood pressure, selection of anatomical targets and utilization of MER [8,10,12,14,16].

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Logistic regression analysis.</th>
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<tbody>
<tr>
<td>Variable</td>
<td>Significance</td>
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<tr>
<td>Sex</td>
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<tr>
<td>Age</td>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Anatomical target</td>
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MER-microelectrode recording.
the present study showed that there was no significant correlation between age and ICH occurrence, which is consistent with the report of Binder et al. [8], but Ben-Haim et al. [16] found that the mean age of hemorrhagic patients was significantly older than that of patients without hemorrhage ($P = 0.02$). Sansur et al. [12] also reported that age was a factor contributing to hemorrhage. There appears to be no significant correlation between sex and hemorrhage. But Sansur et al. [12] reported that ICH occurrence was significantly higher in male patients. Most studies agree that hypertension is a risk factor for cerebral hemorrhage [10,12,14], which is consistent with our finding. The reason may be related to vasosclerosis of hypertensive patients. Terao et al. [13] pointed out that the frequency of cerebral hemorrhages varied with target points, because of different anatomy and supply of cerebral vessels in different target points. We found no such a correlation in the present study.

Whether the use of microelectrode recording increases the incidence of ICH remains unanswered. Some reports suggest that there is no significant relationship between hemorrhage and MER [9,12], and others are more cautious [10,18,20,24,25]. Our results indicate that there was no significant correlation between the number of MER trajectories and ICH occurrence ($P = 0.07$), but the ICH incidence showed a non-significant trend of increasing with the number of microelectrode penetrations. There are two concerns about MER. One is that MER involves multiple penetrations into the brain so that each penetration carries a certain degree of risk. The other is that the sharp microelectrode tip is more liable to penetrate a small artery than the blunt-tipped macroelectrode. Analysis of the actual location of hematoma may help to clarify the exact cause of microelectrode-related hemorrhage. If the hematoma is located in the cortex or superficial area, it is mostly likely caused by the microelectrode guide cannula, and if the hematoma is located deep, it is more likely caused by the sharp tip of the microelectrode. But as most MER patients in our series received ablation, such a comparison may be difficult in light of the potential confounds with radiofrequency lesions.

4.4. Application value of MER

As MER may cause cerebral hemorrhage and is a long procedure, its application value deserves discussion. MRI examination combined with intra-operative stimulation testing is considered to be sufficient to verify the location of the target site in many reports [7,11,14,17]. A literature review by Hariz et al. [17] indicated that in comparison to MRI-based macrostimulation technique, MER technique may increase the risk of ICH without enhancing the accuracy. We believe that the value of MER varies with different target sites. It is more appropriate for Gpi because it can clearly define the target boundary by recording the cellular electric discharge. MER is also critically important to avoid damage to the optic tract.

However, MER is less valuable for Vim and STN. The electrode needs to be adjusted even with the use of MER during the procedure in some patients [12,15,19,26]. The electrode misplacement rate was 9% (14/155 procedures) according to Lyons et al. [19], and 2.2% (6/272 procedures) according to Seijo et al. [22]. In the early stage of our study, MER was routinely used in DBS. Nevertheless, later in the study 87 patients who did not receive MER were checked by intra-operative MRI scan with the stereotactic frame. Deviation of the actual target from the tentative target was detected in 21 of 87 patients, and adjustment was made accordingly during the procedure without causing cerebral hemorrhage.

4.5. How to lower the occurrence of ICH in DBS

DBS has been widely used in the treatment of PD and other movement disorders. How to lower ICH in DBS is one of the greatest concerns in neurosurgery [8,18]. The occurrence of ICH in our patients who received DBS was lower than that reported in the literature [8,9,13,21–23]. We attributed the lower rate to the following reasons: 1) careful treatment of coagulation dysfunction and hypertension prior to surgery; 2) incision of the arachnoid and pia mater performed under direct vision; cautious and proper insertion of the electrode in the gyrus avoiding the vascular surface of the brain; 3) strict adherence to the protocol, precise control of the equipment, and minimization of penetrations to the brain tissue during DBS electrode implantation; and 4) application of intra-operative MRI scan with stereotactic frame instead of MER during operation to avoid MER-related cerebral hemorrhage.

5. Conclusions

The clinical data in our study indicate that radiofrequency thermocoagulation is the most significant risk factor for ICH in the surgical treatment of PD. The incidence of ICH is high in hypertensive patients even when blood pressure is well controlled. Although there was no significant correlation between the number of MER trajectories and ICH occurrence ($P = 0.0705$), the risk of ICH would increase by 0.457 times when one more trajectory MER is added. Application of intra-operative MRI with the stereotactic frame instead of MER is recommended in stereotactic surgery because of its advantage of retrieving intra-operative positioning errors and avoiding MER-related ICH.

References


