Reducing hemorrhagic complications in functional neurosurgery: a large case series and systematic literature review

Clinical article

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Object. Hemorrhagic complications carry by far the highest risk of devastating neurological outcome in functional neurosurgery. Literature published over the past 10 years suggests that hemorrhage, although relatively rare, remains a significant problem. Estimating the true incidence of and risk factors for hemorrhage in functional neurosurgery is a challenging issue.

Methods. The authors analyzed the hemorrhage rate in a consecutive series of 214 patients undergoing image-guided deep brain stimulation (DBS) lead placement without microelectrode recording (MER) and with routine postoperative MR imaging lead verification. They also conducted a systematic review of the literature on stereotactic ablative surgery and DBS over a 10-year period to determine the incidence and risk factors for hemorrhage as a complication of functional neurosurgery.

Results. The total incidence of hemorrhage in our series of image-guided DBS was 0.9%: asymptomatic in 0.5%, symptomatic in 0.5%, and causing permanent deficit in 0.0% of patients. Weighted means calculated from the literature review suggest that the overall incidence of hemorrhage in functional neurosurgery is 5.0%, with asymptomatic hemorrhage occurring in 1.9% of patients, symptomatic hemorrhage in 2.1% and hemorrhage resulting in permanent deficit or death in 1.1%. Hypertension and age were the most important patient-related factors associated with an increased risk of hemorrhage. Risk factors related to surgical technique included use of MER, number of MER penetrations, as well as sulcal or ventricular involvement by the trajectory. The incidence of hemorrhage in studies adopting an image-guided and image-verified approach without MER was significantly lower than that reported with other operative techniques (p < 0.001 for total number of hemorrhages, p < 0.001 for asymptomatic hemorrhage, p < 0.004 for symptomatic hemorrhage, and p = 0.001 for hemorrhage leading to permanent deficit; Fisher exact test).

Conclusions. Age and a history of hypertension are associated with an increased risk of hemorrhage in functional neurosurgery. Surgical factors that increase the risk of hemorrhage include the use of MER and sulcal or ventricular incursion. The meticulous use of neuroimaging—both in planning the trajectory and for target verification—can avoid all of these surgery-related risk factors and appears to carry a significantly lower risk of hemorrhage and associated permanent deficit. (DOI: 10.3171/2011.8.JNS101407)

KEY WORDS • functional neurosurgery • deep brain stimulation • stereotactic technique • hemorrhage

FUNCTIONAL neurosurgical procedures are rarely life saving and are mainly aimed at improving quality of life in patients with progressive, though essentially nonfatal, neurological illness. Further neurological disability or death caused by such an intervention certainly constitutes a dire scenario. Despite their relatively low incidence, hemorrhagic complications carry by far the highest risk of devastating neurological outcome. Not all hemorrhages lead to clinically relevant problems, but lowering the overall incidence of all hemorrhages is likely to reduce the risk of those that cause permanent neurological disability or death.

Given the low frequency of hemorrhage in functional neurosurgery, estimating its true incidence and identifying risk factors are challenging. We reviewed the hemorrhage rate in a consecutive series of patients undergoing...
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functional neurosurgery via an image-guided approach at our institution. Evidence from the literature was also examined to determine the incidence and risk factors for hemorrhage as a complication of functional neurosurgery.

Methods

Our Consecutive Series of Image-Verified DBS Procedures

The medical records and postoperative imaging studies of all patients undergoing frame-based image-guided DBS surgery at the National Hospital for Neurology and Neurosurgery between November 2002 and June 2010 were reviewed. Magnetic resonance imaging–guided electrode implantation was performed under local or general anesthesia using the Leksell Coordinate Frame (Model G, Elekta Instrument AB).22 Preoperative stereotactic 1.5-T MR images were obtained in all patients (Sigma MR imaging scanner, General Electric). Contiguous slices, 2 mm in thickness, were acquired through the target area; T1-weighted 3D volumetric images of the whole brain were obtained using spoiled gradient–recalled acquisition in all patients. The intended target determined the nature of additional MR sequences obtained.31,35,70 Images were imported to a commercially available planning station (FrameLink, Medtronic). A pericoronal entry point was planned. Image reconstruction along the trajectory allowed rapid and accurate assessment of whether the planned trajectory would involve a sulcus or ventricle. The exact entry and target point were subsequently modified to maintain a parenchymal trajectory while maximizing the length of the trajectory within the visualized target structure. The intended coordinates and planned arc and ring angles were recorded.

At surgery, patients were positioned supine with their head slightly elevated (approximately 15°), and the head and frame were supported by a sand-filled vacuum pillow. A 14-mm bur hole was placed in line with the planned trajectory and proprietary lead-anchoring systems fixed to the skull (enclosed bur-hole ring and cap early in the series; Stimloc, Medtronic, more recently). The dural and pial entry points were coagulated with bipolar electrocautery and opened sharply. Dynamic impedance monitoring was always employed while introducing a 1.5- or 2.2-mm blunt-tip monopolar brain lesion electrode to the target (Leksell, Elekta). This monitoring confirmed that the trajectory did not involve the ventricle as well as confirming the presence of gray matter in the target region.68,71 After withdrawal of the monopolar brain lesion electrode, a quadripolar DBS electrode (Model 3389 DBS lead, Medtronic) was placed down the same track. Cerebrospinal fluid loss and associated brain shift were minimized by flooding the surgical field with saline and sealing the dural defect as soon as practical with fibrin glue (Tisseel VH Fibrin Sealant, Baxter AG) after implantation of the electrode. The DBS electrode was then secured with the lead-anchoring system. Microelectrode recording was not used. In those patients undergoing surgery under local anesthesia, symptoms were assessed for the presence of a microlesion-introduction effect, as well as by intraoperative stimulation through the contacts of the DBS electrode by an experienced neurologist.11

Immediate postoperative stereotactic MR imaging with the Leksell frame in place was obtained to assess electrode position and screen for surgical complications. The specific absorption rate was limited to < 0.4 W/kg. As with other large series, no complications related to the postoperative MR imaging acquisition occurred.43,47,60

Literature Review

During the past 10 years, DBS has replaced lesioning as the predominant treatment in functional neurosurgery.29 We therefore conducted an online PubMed search of the English-language human literature published during the 10-year period from July 1, 2000, through June 30, 2010, using the following search parameters: (“deep brain stimulation” OR “functional neurosurgery”) AND (“hemorrhage” OR “bleed”). Papers were reviewed and further articles selected on the basis of cited references.

Only papers that specifically reported hemorrhagic complications were included. In view of the relatively low hemorrhagic rate generally reported in functional procedures, smaller series that included less than 40 patients were not considered further. When a large overlap of patient reporting from the same institution seemed probable, only the largest report with the most comprehensive assessment of hemorrhagic complications was selected.

Statistical Analysis

The Fisher exact test was used to compare the incidence of hemorrhage in studies using an image-guided and image-verified approach without MER with that reported in publications documenting the use of other peroperative techniques. The level of significance for all analyses was chosen at p < 0.05.

Results

Hemorrhage in our Series of Image-Guided DBS Procedures

Four hundred seventeen electrodes were implanted in 214 patients (130 male) through 230 consecutive, frame-based, image-guided DBS procedures (141 in male patients; mean [± SD] patient age at time of surgery was 51.6 ± 14.4 years). The primary indications are presented in Table 1. Bilateral electrodes were implanted during a single session in 186 procedures. Two patients underwent staged bilateral electrode implantation. In 1 patient with chronic pain, 2 electrodes were implanted into a single side in 1 procedure (in the sensory thalamus and periventricular and periaqueductal gray). Unilateral implants were performed in another 39 procedures. Four electrodes were immediately relocated in 4 patients during the initial procedure due to suboptimal locations on the intraprocedural MR images.

One patient underwent 3 implantation procedures: after bilateral STN DBS for PD, the left STN DBS electrode was re-sited 7 months postoperatively in view of suboptimal outcome on that side; 2 years later, bilateral pallidal DBS was performed in an attempt to address the development of painful dyskinesia-dystonia. Eleven patients underwent 2 electrode implantation procedures: 1

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patient with PD who developed painful dystonia underwent bilateral GPi DBS 3 years after having received bilateral STN DBS; 1 patient underwent bilateral anteromedial GPi DBS after previously undergoing unilateral posterior ventral pallidal DBS for Tourette syndrome; 4 patients (2 with PD, 1 with dystonia, 1 with cervical dystonia) underwent unilateral and 1 patient (with PD) bilateral electrode retargeting because of suboptimal outcome; relocation of an electrode to a different target because of suboptimal outcome was performed in 2 patients; 2 patients (1 with dystonia, 1 with PD) underwent extraction of bilateral electrodes and reimplantation because of ascending infection from an infected impulse generator site; 1 patient underwent removal of an electrode because of erosion through the scalp and underwent retargeting via a parietal approach. Therefore, excluding staged bilateral implantation, multiple DBS procedures were performed in 5.6% of patients.

All patients underwent immediate postoperative imaging after electrode implantation. A stereotactic MR imaging study could not be performed in 5 procedures. In 3 of these cases, a stereotactic CT scan was performed because of MR imaging contraindications. In the other 2 cases, a stereotactic MR imaging study could not be performed for technical reasons; in both instances nonstereotactic MR imaging was obtained by the end of the first postoperative day.

None of the immediate postoperative scans revealed evidence of hemorrhage. However, there were 2 small delayed cortical hemorrhages in this series. One 49-year-old patient with PD and a history of well-controlled hypertension suffered a postoperative seizure and a small delayed symptomatic cortical hemorrhage was evident on CT (Fig. 1 Left). A mild postictal facial weakness resolved within a few days. A small delayed asymptomatic cortical hemorrhage was detected in a 61-year-old man with PD who underwent bilateral STN DBS under local anesthesia. There were no risk factors and no hemorrhage was visible on the immediate postoperative MR imaging. Mild dysarthria developed on the 1st postoperative day and prompted a CT of the brain that revealed a small delayed superficial cortical hemorrhage (Fig. 1 Right). The dysarthria resolved within 1 month of surgery and was thought to be unrelated to the hemorrhage since it could be reproduced by high-voltage stimulation on long-term follow-up. There were no other hemorrhagic complications in this series.

The perioperative rate for hemorrhage was therefore 0.5% per electrode and 0.9% per procedure. In only 1 patient (0.5%) was the hemorrhage symptomatic and these symptoms had resolved within a week of onset. In view of the low incidence of hemorrhage, statistical analysis of underlying risk factors for hemorrhage within this series was not possible.

Ablative Procedures

During the study period, 3 lesioning procedures were also performed at our institution. These were performed under local anesthetic, using dynamic impedance guidance and macroelectrode stimulation but without MER. None of these patients suffered a hemorrhage. This small number of procedures was not considered relevant to risk analysis.

Incidence of Hemorrhage in the Literature

The reported incidence of hemorrhagic complications in the recent literature is summarized in Table 2. Literature reviews appear at the top of the table1,14,28,39,51 and series with 40 or more patients are presented below.4–8,10,12,15,16,19,21,23–28,33,37,38,40,42,47,49,50,52,56,59,61,63,65,67 Weighted means

<table>
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<tr>
<th>Primary Pathology</th>
<th>No. of Procedures</th>
<th>No. of Patients</th>
<th>No. of Electrodes</th>
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<td>133</td>
<td>124</td>
<td>250</td>
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<td>PSP</td>
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<td>2</td>
<td>2</td>
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<tr>
<td>dystonia</td>
<td>70</td>
<td>66</td>
<td>133</td>
</tr>
<tr>
<td>tremor</td>
<td>9</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Tourette syndrome</td>
<td>5</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>chronic pain</td>
<td>7</td>
<td>6</td>
<td>8</td>
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<tr>
<td>cluster HA/SUNCT</td>
<td>4</td>
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</table>

* A total of 417 electrodes were placed during 230 procedures. Anatomical targets included the subthalamic nucleus, GPi (posteroventral and anteromedial), zona incerta, Vim, ventralis oralis anterior, ventral posterolateral, ventral posteromedial nuclei of the thalamus, periventricular and periaqueductal gray, posterior hypothalamus and pedunculopontine nucleus. Abbreviations: HA = headache; PSP = progressive supranuclear palsy; SUNCT = short-lasting unilateral neuralgiform headache with conjunctival injection and tearing.

<table>
<thead>
<tr>
<th>Procedures</th>
<th>No. of</th>
<th>No. of</th>
<th>No. of</th>
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<td>PD</td>
<td>133</td>
<td>124</td>
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<td>PSP</td>
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<tr>
<td>dystonia</td>
<td>70</td>
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<td>tremor</td>
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<tr>
<td>Tourette syndrome</td>
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</table>

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**TABLE 2: Summary of the incidence of hemorrhage in the published literature**

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Patients</th>
<th>Total (%)</th>
<th>Asymptomatic (%)</th>
<th>Symptomatic (%)</th>
<th>Permanent Deficit (%)</th>
<th>MER Used</th>
<th>Type of Procedure</th>
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<td>26 (1.7)</td>
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<td>334</td>
<td>—</td>
<td>—</td>
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<td>Hamani et al., 2005</td>
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<td>—</td>
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<td>86</td>
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<td>—</td>
<td>—</td>
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<td>49</td>
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<td>3 (1.6)</td>
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</table>

* ANT = anterior nucleus of the thalamus; thal = thalamus.
† MER used in 860 patients; symptomatic hemorrhages do not include deaths.
‡ MER used in 365 of 563 patients.
§ Resulting in 4 fatalities.
¶ MER used in an unspecified number of patients.
** Documented procedures not patients and only included hemorrhage > 5 mm.
†† Resulting in 1 death.
‡‡ MER used in 104 patients.
§§ Center(s) known to use MER routinely although not stated in manuscript.
¶¶ Resulting in 2 deaths.
a MER was not used in 87 of 644 patients.
b Including 3 “strokes” taken to represent permanent deficit.
calculated from the included patient series suggest that the overall incidence of hemorrhage was 5.0%, asymptomatic in 1.9% of cases, symptomatic in 2.1% and resulting in permanent deficit or death in 1.1%. Because some publications do not report on all types of hemorrhage, these figures are derived from different patient populations and do not necessarily “add up.”

Risk Factors for Hemorrhagic Complications

Numerous risk factors have been proposed for hemorrhagic complications during functional neurosurgery procedures.

Hypertension. Xiaowu et al.67 examined the risk factors for hemorrhage in their large series of 644 patients undergoing lesioning, DBS surgery, or both. Logistic regression analysis suggested that in hypertensive patients the risk of bleeding was 2.5 times that in normotensive patients (p < 0.05). Hypertension was found to be a significant risk factor for hemorrhagic complications by Higuchi and Iacono,34 Gorgulho et al.,25 Sansur et al.,56 and Elias et al.,17 but not by Ben-Haim et al.4

Age. Sansur et al.56 reported on 259 cases in which patient age was significantly associated with hemorrhage (mean age of patients with symptomatic hemorrhage 65 years vs 41 years for those without). Ben-Haim et al.4 also found that the mean age of patients with hemorrhage was significantly higher than that of patients without hemorrhage (64.2 ± 9.5 vs 53.3 ± 15.9 years, respectively; p = 0.02). In a multicenter study involving 1183 patients, Voges et al.65 reported age of 60 years or greater as a risk factor for hemorrhage but did not present the raw data or statistical analysis on which they based this conclusion. Ory-Magne et al.30 examined the effect of age on outcome of STN DBS in PD. They reported a high incidence of bleeding (8.9%) and mortality (4.4%) in their series of 45 patients, noting that only elderly patients with PD experienced symptomatic hemorrhage and that there was a significant association between occurrence of bleeding and age (Mann-Whitney U-test, p = 0.003).

Terao et al.61 reported that the mean age of patients with hemorrhage did not differ significantly from that of patients without hemorrhage (60.5 ± 7.1 years vs 56.1 ± 14.9 years, respectively; p = 0.35, 1-way ANOVA). Seijo et al.,24 Binder et al.,7 Elias et al.,17 and Xiaowu et al.67 reported no statistically significant correlation between intracranial hemorrhage and age.

Gender. Sex difference did not significantly contribute to hemorrhage rates in the studies by Ben-Haim et al.,4 Gorgulho et al.,25 Seijo et al.,24 Elias et al.,17 and Xiaowu et al.67 However, Sansur et al.56 found male sex to be significantly associated with hemorrhage.

Diagnosis. Sansur et al.56 suggested that a diagnosis of PD was associated with increased risk of hemorrhage. Elias et al.17 found that the overall incidence of vascular complications in patients with PD was triple that seen in dystonia and tremor (8.0% vs 2.5%) but this difference did not reach statistical significance. Binder et al.7 and Ben-Haim et al.4 failed to find an association of hemorrhage with disease process.

Previous use of Anticoagulants. Sansur et al.56 examined 143 patients; 23 patients (16%) had previously used anticoagulant medication such as aspirin. This was not associated with a higher risk of observed hemorrhage.

Use of MER. In their 2001 review of the literature on pallidotomy, Alkhani and Lozano1 found that centers using MER reported a significantly higher incidence of cerebral hemorrhage than those that employed macroelectrode stimulation (p = 0.003). They noted that death after pallidotomy (0.4%) was usually secondary to the occurrence of a large intracerebral hemorrhage. These results were echoed by Palur et al.51 in 2002 who reported that MER was associated with a significantly higher (p = 0.012) hemorrhage rate compared with macroelectrode stimulation in patients undergoing unilateral pallidotomy for PD. In their systematic review on pallidotomy for PD, de Bie14 reported that the frequency of stroke was 4.9% higher when MER was employed. In his review on MER in surgery for movement disorders, Hariz26 concluded that MER techniques were relatively safe, but non-MER techniques, based on macrostimulation-guided surgery, were at least 5 times safer. These findings were again confirmed by Higuchi and Iacono34 in a large single-center series involving 796 patients undergoing pallidotomy: MER was performed in 73 patients and its use was strongly correlated with intracerebral hemorrhage, with an approximately 4-fold increase in the risk of hemorrhage. Gorgulho et al.25 reported on 178 patients, MER being used in 104; a slightly higher incidence of hemorrhage was noted in patients undergoing surgical procedures with MER (2.9% of patients undergoing MER vs 1.4% without MER; not statistically significant). However, the combination of MER and hypertension was found to significantly increase the incidence of bleeding. In the macroelectrode group, no additional risk of hemorrhage was detected, even in patients with hypertension. Ben-Haim et al.4 reported 7 hemorrhages (a rate of 5.4%), 2 asymptomatic (1.5%), 5 symptomatic (3.8%), in 130 patients undergoing 246 MER-guided electrode implantation procedures. They suggested that a new microelectrode design significantly decreased the number of hemorrhages (p = 0.04). It is worth noting that the same group reported only 2 asymptomatic hemorrhages (a rate of 2.7%) when performing non–MER-guided unilateral pallidotomy in 75 patients 9 years earlier.18

Number of MER Penetrations. In their 2001 article, the Deep-Brain Stimulation for Parkinson’s Disease Study Group14 reported that the number of microelectrode passes used to determine target location significantly correlated with the risk of hemorrhage. The 127 patients without hemorrhage had a mean of 2.9 ± 1.8 passes, as compared with 4.1 ± 2.0 passes among the 7 who had hemorrhage (p = 0.05). In a review of 280 cases (with a 2.2% rate of symptomatic hemorrhages and a 3.6% rate of asymptomatic hemorrhages), Binder et al.7 noted that there was a trend toward a higher number of MER penetrations in patients with hemorrhage compared with those without hemorrhage. Although this trend was not statistically significant, the authors suggested that lack of significance was related to the size of the data set, rather than a true
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absence of risk associated with MER. Regression analysis estimated the increased risk per MER penetration as 1.3 (95% CI 0.9–1.8). Mikos et al.34 reported a 4.3% incidence of hemorrhage in 115 patients undergoing DBS; pathological changes and hemorrhage were the most common reasons for delayed discharge in this study. Delayed discharge from hospital was also significantly associated with the number of MER passes (p = 0.012). Elias et al.17 reported no significant difference in the mean number of MER penetrations between the group without complications (1.08 ± 0.87, 163 patients) and the group with cortical hemorrhage (1.6 ± 0.89, p = 0.189; 5 patients), patients with intraventricular hemorrhage (1.60 ± 0.55, p = 0.130; 5 patients), or patients with symptomatic hemorrhage (1.75 ± 0.96, p = 0.186; 4 patients). However, the mean number of penetrations was higher in each group with hemorrhagic complications, suggesting an overall trend toward a higher number of MER penetrations in patients with hemorrhagic complications. In their study of 130 patients undergoing STN DBS, Seijo et al.59 observed no statistical significance between hemorrhage and the number of MER trajectories. The number of microelectrodes passed did not significantly contribute to hemorrhage rates in the 2009 study by Ben-Haim et al.4 Xiaowu et al.67 also reported a trend toward an association between the number of MER trajectories and intracerebral hemorrhage, but this did not reach statistical significance (p = 0.07).

Sulcal Involvement by the Trajectory. Elias et al.17 examined the sulcal proximity of the electrode trajectory to the cortical complication rate. Sulcal proximity was not statistically associated with cortical hemorrhage (χ² = 1.879, p = 0.170). However, sulcal trajectories did correlate with the overall cortical complication rate: 11 (92%) of 12 events involved electrodes in proximity to a sulcus (χ² = 11.57, p = 0.001).

Ventricular Involvement by the Trajectory. Overall hemorrhage rate was found to be significantly associated to a surgical trajectory traversing the ventricle.4 Not surprisingly, ventricular incursion was also found to hold a significant association with intraventricular hemorrhage: 10.8% of ventricular penetrations resulted in intraventricular hemorrhage, half of which produced a focal deficit.4 Elias et al.17 observed asymptomatic intraventricular hemorrhage in 4.0% of ventricular penetrations.

Deep Brain Stimulation Versus Lesional Surgery. Xiaowu et al.67 examined the risk factors for hemorrhage in their large series of 644 patients undergoing lesioning, DBS or both. The risk of hemorrhage with ablation was 5.4 times that in DBS and was statistically significant (p < 0.05). Terao et al.66 also observed that hemorrhage was almost 5 times more frequent after lesioning than after DBS. However, Gorgulho et al.25 pointed out that large series of ablative procedures have demonstrated no or a very low rate of hemorrhage, suggesting that radiofrequency lesioning alone may not be a causal factor for hemorrhage. Favre et al.19 and Blomstedt and Hairz9 failed to find a significant difference in hemorrhage risk between lesional surgery and DBS.

Anatomical Target. Ben-Haim et al.4 reported a trend for increased rates of hemorrhage when the Vim was targeted (p = 0.057). Terao et al.66 also reported an increased risk of bleeding with radiofrequency lesions in the Vim. However, Binder et al.7 detected a different effect of brain target with 1 hemorrhage after thalamic DBS (1.2%) compared with 6 hemorrhages in the STN group (2.2%) and 9 hemorrhages in the GPI group (7.0%). Gorgulho et al.25 and Xiaowu et al.67 found no correlation of hemorrhage rate with target.

Incidence of Hemorrhage With Image-Verified DBS in the Literature

The Fisher exact test revealed a significantly lower incidence in all types of hemorrhage (p ≤ 0.004) when utilizing an image-guided and image-verified approach without MER (in the present study and 3 others5,47,52) compared with that reported with the use of other operative techniques (Table 3).

Discussion

Hemorrhage is one of the most devastating complications in functional neurosurgery. This review confirms that literature published over the past 10 years suggests that hemorrhage, although relatively rare, still remains a significant problem. A number of risk factors for hemorrhage during functional neurosurgery have been examined. The most convincing patient factors include hypertension and age. The most compelling factors in surgical methodology include the use of MER and the number of MER penetrations, as well as a trajectory that involves a sulcus or ventricle. The use of MR imaging for guidance and verification of DBS electrode placement avoids these surgery-related risk factors. This may explain why reported hemorrhage rates with image-verified DBS surgery are among the lowest in the literature.

Reducing the Risk of Hemorrhage With an Image-Verified Approach

The incidence of hemorrhage in the present series of 214 patients undergoing MR imaging–verified DBS surgery without MER was 0.9%, asymptomatic in 0.5%, symptomatic in 0.5%, and causing permanent deficit in 0.0% of patients. These percentages are similar to hemorrhage rates of 3 other studies that exclusively employed image-guided targeting without MER.4,47,52 Hemorrhage rates of all types were significantly lower than in other reported series (p ≤ 0.004).

Theoretically, an image-based approach to functional neurosurgery may be expected to reduce the risk of hemorrhage in various ways. Planning and performing a single trajectory that avoids the cerebral sulci and ventricles would avoid the enclosed vessels, theoretically minimizing the risk of hemorrhage. Functional neurosurgeons have not always had the luxury of being able to plan a surgical trajectory on computer-generated reconstructions of high-resolution MR images. Before this technology became available, perhaps less emphasis was placed on the entry point and precise surgical trajectory.
4% of ventricular penetrations. Ben-Haim et al.4 reported served an asymptomatic intraventricular hemorrhage in the target.17 It is important to note that planning an entry point to penetrate the ventricles should proceed in a stepwise manner with the planned trajectory being reestablished at every tissue layer (scalp, skull, dura mater, and pia mater) to ensure fidelity of the surgical trajectory to the planned one.

Numerous authors have also advocated trajectories that avoid the ventricles.2,3,11,13,26,32,44,54,69 These recommendations were initially made on neuroanatomical grounds without the support of clinical data54 but have recently been confirmed in clinical practice.17 The individual complexity of the sulcal pattern and obliquity of the surgical trajectory require the acquisition of stereotactic images (CT or MR) and image manipulation with commercially available planning software that allows reconstruction along the proposed trajectory to ascertain the avoidance of sulci and enclosed blood vessels. Incursion into sulcus or ventricle can often be avoided by reconsideration of the planned entry point.

In some instances it may be impossible to access certain targets satisfactorily without involving sulci or ventricles. A transventricular route may have to be considered for other DBS targets (for example, the pedunculopontine nucleus in parkinsonism, the anterior nucleus of the thalamus in epilepsy).27,64,70 In such instances, the use of contrast media in the acquisition of images may provide additional information on the location of vascular structures; indeed, some authors advocate the routine use of enhanced imaging prior to surgery.32,46 Another consideration is the use of a blunt tip probe that may push aside vessels or choroid plexus encountered en route to the target without damaging them.

Improving the accuracy of initial image-guided targeting is also likely to reduce the number of brain penetrations per procedure, a theoretical advantage that may also reduce the hemorrhage risk. A clear association between ventricular involvement, decreased targeting accuracy and requirement for multiple brain passes has also been demonstrated.69 Other methods of improving accuracy of image-based functional neurosurgery are also likely to reduce the requirement for multiple brain penetrations.56 In this series, a second brain pass was performed to correct initial suboptimal electrode location in 10 (2.4%) of 417 electrodes and 9 (4.2%) of 214 patients.

Incidence of Hemorrhage in the Literature

Hemorrhage leading to permanent deficit is arguably the most clinically relevant problem. Of the systematic reviews available in the 10-year period, the highest rate was reported by de Bie et al.24—9 out of 334 patients, that is, 2.7% or 1 in 37, a ratio that prompted this review to focus on reports that detail studies of 40 patients or more. This approach also allowed the inclusion of a large number of patients (5823 patients) and, at the same time, limited data duplication. The incidence of all types of hemorrhage was similar between the systematic reviews, as were the weighted means calculated from the patient series (Table 2).

<table>
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<th>TABLE 3: Comparison of types of hemorrhage rates in published studies using a strict image-guided approach versus other methods*</th>
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<td><strong>Factor</strong></td>
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* The observed figures were compared with the expected figures using the Fisher exact test. Observed hemorrhage rates are significantly lower than expected for all hemorrhage types in the image-guided studies (p ≤ 0.004). Abbreviation: Im-G = strict image-guided and image-verified approach without MER.
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Patient-Related Risk Factors for Hemorrhage

Of all the patient factors examined, hypertension and age carry the most convincing associations with hemorrhage. Hypertension was a statistically significant factor in 5 studies.\textsuperscript{17,25,34,56,67} One study reported that the combination of MER and hypertension significantly increased the incidence of bleeding but that when MER was not used no additional risk of hemorrhage was detected in patients with hypertension.\textsuperscript{23} Only 1 study (involving 130 patients) failed to reveal any association with hypertension.\textsuperscript{4}

Increasing age was associated with a significant increase in the incidence of hemorrhage in 4 studies.\textsuperscript{4,50,56,65} One study reported a trend that did not reach statistical significance.\textsuperscript{61} Four other studies failed to document a significant effect of age on hemorrhage risk.\textsuperscript{7,17,59,67} Reports of male sex and a diagnosis of PD as risk factors for hemorrhage are inconsistent.\textsuperscript{4,17,25,56,59,67} The 2 hemorrhages in the present study occurred in male patients, a 49 year old and a 61 year old. Only one of these patients had a history of pharmacologically well-controlled hypertension and both had a diagnosis of PD. The small number of hemorrhages made it impossible to perform a meaningful statistical analysis.

Surgery-Related Risk Factors for Hemorrhage

A number of factors related to the surgical technique appear to be associated with an increased risk of hemorrhage: the use of MER and the number of MER penetrations, as well as incursion into a sulcus or ventricle. Opinion is divided as to the risk associated with lesioning as opposed to DBS surgery. Anatomical target does not appear to be consistently associated with hemorrhage risk across studies.

Microelectrode Recording. The association of MER with an increased risk of hemorrhage is currently a widely debated issue. A number of reviews have concluded that MER is associated with an increased risk of hemorrhage.\textsuperscript{14,30,51} Other authors report strong correlations between MER use and hemorrhage.\textsuperscript{25,34} A significant association between number of MER passes and hemorrhage rate was also reported by the DBS study group,\textsuperscript{15} and trends that approached but did not reach significance were reported by others.\textsuperscript{7,61} with some authors suggesting that significance would have been reached had the sample size been large enough.\textsuperscript{7}

Three previous studies that do not use MER have demonstrated very low hemorrhage rates.\textsuperscript{9,47,52} It has been suggested that the low hemorrhage rate in the Montpellier study may be explained by the large number of young dystonic patients in that study and inclusion of only 25 patients with PD from a total of 194.\textsuperscript{47} However, this argument does not apply to the other 2 studies or to the present series.

A randomized controlled trial comparing MER-guided to non–MER-guided surgery is desirable but may not be practically feasible. However, a significant reduction in hemorrhage rate can be expected when adopting an image-guided and image-verified approach without MER (as in the present study and 3 others\textsuperscript{9,47,52}).

Incursion Into Sulcus or Ventricle. Avoidance of sulcal and ventricular involvement by the trajectory is likely to reduce the risk of complications by avoiding surgical trauma to the enclosed vessels. Recent publications have demonstrated that this probably holds true in clinical practice.\textsuperscript{17,22}

Deep Brain Stimulation Versus Ablative Surgery. It has been suggested that lesioning surgery carries a higher risk of hemorrhage than DBS surgery but this stance has been contested.\textsuperscript{9,25,61} One mechanism that would explain the former observation would be adherence of the coagulum to the radiofrequency probe and rupture of vessels on probe withdrawal. However, the method of coagulation (rate of temperature increase, duration of coagulation and maximal temperature reached) may all have a bearing on this observation in clinical practice. Differing practices in lesion production may explain the inconsistent observations with regard to this surgical factor.

Limitations and Relevance of the Study

It is difficult to design and perform studies that can achieve the statistical power necessary to demonstrate risk factors for low-probability events. Nevertheless, establishing an evidence base for risk factors that lead to rare but serious events is an important exercise. This review of the literature and analysis of hemorrhagic risk has numerous limitations that afflict any study of this nature. These include publication bias, unintended inclusion of repeated data, and unaccounted for differences in patient populations. Despite these limitations, the review provides a summary of the best available evidence to date with respect to avoidance of hemorrhagic complications in functional neurosurgery. Patient factors cannot be altered other than statistically by the patient selection process. However, the image-guided targeting and verification approach presented here would theoretically avoid all of the most compelling risk factors related to the surgical procedure. Analysis of the published literature suggests that these theoretical advantages translate into statistically significant practical advantages in terms of patient safety.

It may be argued that improved safety of an image-verified approach is offset by reduced efficacy. However, there does not appear to be any loss of efficacy with an image-guided approach to functional neurosurgery; outcomes of image-guided approaches to pallidotomy, pallidal DBS for dystonia, and STN DBS for PD compare favorably to those reported in other published series.\textsuperscript{13,22,51,53,62} In a series of 79 consecutive patients undergoing an image-guided approach to STN DBS at our unit, the mean overall improvement from baseline in the Unified Parkinson’s Disease Rating Scale III off-medication motor score was 52% and the hemorrhage rate was 0%.\textsuperscript{22} This compares favorably with the results of a recent meta-analysis of open-label studies (21 patient populations), where the mean improvement from baseline after STN DBS was 52% and the hemorrhage rate was 3.9%.\textsuperscript{38} Indeed, improvement after reoperation in patients with suboptimal outcomes due to poor electrode location has been obtained without the use of MER.\textsuperscript{35}
Many functional neurosurgery teams use MER to “refine” the surgical intervention, and there is no doubt that MER is an important research tool. Nevertheless, evidence that MER is superior to a meticulous image-guided approach in terms of clinical outcome is lacking.

The importance of safety in a quality-of-life procedure cannot be overstated. This is especially true for novel indications when the benefits of surgery are still under investigation as exemplified by a pilot study involving 6 patients undergoing MER-guided DBS for cluster headache in which 1 patient developed massive hematomas along the surgical trajectory with intraventricular extension leading to a fatal outcome, or a study involving 17 young patients undergoing STN DBS for obsessive-compulsive disorder in which 1 patient had a permanent hand paresis due to hemorrhage.48

Conclusions

This study summarizes the risk factors for hemorrhage during functional neurosurgery procedures. Well-established patient factors include increased age and a history of hypertension. Surgical methodologies associated with hemorrhage include the use of MER and incursion by the trajectory into a sulcus or ventricle. The hemorrhage risk in our present case series of 214 patients undergoing image-guided frame-based DBS electrode implantation without MER is among the lowest in the literature. Statistical analysis suggests that image-guided and image-verified techniques carry a significantly lower risk of hemorrhage than other surgical methodologies. Moreover, the incidence of hemorrhage that led to permanent deficit or death was also significantly lower with an image-guided and verified approach.

Disclosure

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Author contributions to the study and manuscript preparation include the following. Conception and design: Zrinzo, Hariz. Acquisition of data: Zrinzo, Hariz. Analysis and interpretation of data: Zrinzo, Hariz. Drafting the article: Zrinzo. Critically revising the article: all authors. Statistical analysis: Zrinzo, Foltynie. Study supervision: Zrinzo, Limousin, Hariz.

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