Acta Neurochirurgica (2023) 165:3385–3396
https://doi.org/10.1007/s00701-023-05799-w

ORIGINAL ARTICLE

Complications of deep brain stimulation in Parkinson's disease: a single-center experience of 517 consecutive cases

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Received: 11 June 2023 / Accepted: 3 September 2023 / Published online: 29 September 2023

Abstract

Background The number of deep brain stimulation (DBS) procedures is rapidly rising as well as the novel indications. Reporting adverse events related to surgery and to the hardware used is essential to define the risk-to-benefit ratio and develop novel strategies to improve it.

Objective To analyze DBS complications (both procedure-related and hardware-related) and further assess potential predictive factors.

Methods Five hundred seventeen cases of DBS for Parkinson's disease were performed between 2006 and 2021 in a single center (mean follow-up: 4.68 ± 2.86 years). Spearman's Rho coefficient was calculated to search for a correlation between the occurrence of intracerebral hemorrhage (ICH) and the number of recording tracks. Multiple logistic regression analyzed the probability of developing seizures and ICH given potential risk factors. Kaplan-Meier curves were performed to analyze the cumulative proportions of hardware-related complications.

Results Mortality rate was 0.2%, while permanent morbidity 0.6%. 2.5% of cases suffered from ICH which were not influenced by the number of tracks used for recordings. 3.3% reported seizures that were significantly affected by perielectrode brain edema and age. The rate of perielectrode brain edema was significantly higher for Medtronic's leads compared to Boston Scientific's ($X^2(1)= 5.927$, $P= 0.015$). 12.2% of implants reported Hardware-related complications, the most common of which were wound revisions (7.2%). Internal pulse generator models with smaller profiles displayed more favorable hardware-related complication survival curves compared to larger designs ($X^2(1)= 8.139$, $P= 0.004$).

Conclusion Overall DBS has to be considered a safe procedure, but future research is needed to decrease the rate of hardware-related complications which may be related to both the surgical technique and to the specific hardware's design. The increased incidence of perielectrode brain edema associated with certain lead models may likewise deserve future investigation.

Keywords Parkinson's disease · Deep brain stimulation · Intracerebral hemorrhage · Surgical complications: Movement disorder · Hardware failure

Deep brain stimulation (DBS) has proved its efficacy to control major symptoms in Parkinson's disease (PD) and long-term follow-up analysis seems to confirm these results [19, 27, 30, 31, 39].

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Nonetheless, numerous surgical, hardware-related, or infective complications may develop after surgery or during the follow-up period, even years after the DBS surgery. Different investigators have reported their experience about surgical or hardware-related complications [4, 6, 7, 14, 20, 33, 41, 48, 54]. However, long-term follow-up data in a large population are still scarce.

Since more groups are involved in DBS surgeries for movement disorders, and as the indications for deep brain stimulation are in constant expansion [28], it is important to accurately report on adverse events related to DBS to correctly assess the risk-to-benefit ratio.

We therefore reviewed our experience in the performance of 517 consecutive DBS surgeries in parkinsonian patients,

operated by the same neurosurgeon, to identify surgical and hardware-related complications, infections, and delayed adverse medical events. As far as we know, this represents the largest case series of Parkinson's patients that underwent DBS operated by a single surgeon.

Methods

Patient population

Between 2006 and 2021, 517 bilateral or unilateral DBS procedures were performed at our Institution, comprehensive of both first implants or surgeries for reimplants or rescue therapies. Four hundred thirty-three of the surgeries targeted the subthalamic nucleus (STN) (414 as first implants or rescue therapies), 82 the postero-medial globus pallidus internus (GPi) (81 of which were first implants or rescue therapies after STN DBS failure), one in the zona incerta (Zin), and one in the ventralis intermedius medialis (VIM) nucleus. The mean age at surgery was 61 years (range, 35–77 years). All patients underwent neurological and neuropsychological assessment according to CAPSIT prior to surgery. Mean disease's duration was 9.92 years, (± 4.65). Mean follow-up of our study was 4.68 ± 2.86 years.

Data collection

Data were collected in a retrospective manner by reviewing the hospital medical records from the Department of Neurosurgery. The Institutional Review Board approval was not necessary, since we performed standard surgical procedures that are indicated for such neurosurgical conditions.

All the surgical procedures performed, including lead positioning, implantable pulse generator (IPG) placement, and IPG replacement after battery exhaustion, were reviewed to identify adverse events. Complications were defined as any deviation from the normal postoperative course [1]. Complications were divided in (1) procedure-related (intracerebral hemorrhage (ICH), lead mispositioning, cerebrospinal fluid leakage, seizure; post-operative brain edema (either symptomatic or not); and infections) and (2) hardware-related (lead migration/fracture/malfunction, IPG malfunction, IPG migration, extension wire breakage, altered impedances and skin erosion).

Operative technique

In our experience, a preoperative brain 1.5 Tesla magnetic resonance imaging (MRI) is routinely performed in all patients. T1-weighted contrast-enhanced sequences (1mm thick, for surgical planning) and T2-weighted sequences (2 mm in thickness, to better visualize the STN) are used when targeting the STN. When the target selected is the postero-medial GPi, we perform T1-weighted contrast-enhanced imaging (1mm thick, for surgical planning) and proton density sequences (2mm in thickness, to better visualize the GPi). On the day of surgery, a brain computed tomography (CT) is performed after placement of the stereotactic frame. MRI and CT images are transferred to a neuronavigation device; the images are fused, and target coordinates are calculated using the anterior commissure-posterior commissure (AC-PC) plane as anatomical referral.

At the beginning of the surgical procedure, the patient is positioned on the operating table, the frame is secured, and the intra-operative CT scanner is positioned at the level of the head of the patient. A sterile drape covers the CT to separate the operating field from the rest of the room. This implementation was introduced after experience with the mobile fluoroscopic system (C-arm) utilized for intra-operative control. From 2008, we introduced in our center the Medtronic O-arm (Medtronic Sofamor Danek, Memphis, TN, USA). It permits to obtain X-rays imaging of the descending electrodes, and intra-operative 3D X-ray images after definitive electrode positioning [50]. In 2020, the Medtronic O-Arm has been replaced by BrainLab Airo system (BrainLab, Munich, Germany) that consists of a mobile intraoperative CT scanner.

We obtain intraoperative microrecordings (MER) by means of a computer-guided system for simultaneous multitrack recording (Neurostar, Kahnerweg 1,72072 Tubingen, Germany). We started using 4 recording microelectrodes, but in 2009, we reduced the number of the microelectrodes to 3: one microelectrode is inserted in the central track corresponding to the planned trajectory and the other two in the antero-medial and in the antero-lateral tracks, respectively. Microelectrode recordings are obtained starting from a site positioned 10 mm cranially to the planned target and ending 3 mm caudally to the planned target if the selected target is the STN; in case of GPi, the starting site is set at the desired target. Microelectrodes are advanced in 0.5-mm steps. The electrical activity in each position is recorded for about 30 to 60 s. Signals are band-pass filtered (250 Hz to 5 kHz), visualized, and stored in personal computer for further off-line analysis.

After electrode implantation, an intraoperative brain 3D X-rays or CT scan is performed and then transferred to the neuronavigation device, where it is fused with the preoperative CT and MR scan to evaluate the correct electrode position. After confirming the correct electrode positioning, the surgeon internalizes the distal end of cerebral electrodes in a pouch under the cranial skin.

All patients underwent either MRI or CT scans priors to the internalization, to assess the position of the electrodes. Eventually, 2 or 3 days after, the internalization of the IPG is performed. All the procedures were carried out in two

surgical steps. The IPG is allocated in a subcutaneous/submuscular pouch in the subclavian region for aesthetic reason (especially in female patients), whereas in earlier cases, the abdominal wall has been utilized.

Statistical analysis

Descriptive statistics (mean and 95% CI standard deviation) were utilized for continuous variables and frequency percentages for categorical variables. Spearman's Rho coefficient was calculated to search for a correlation between the occurrence of ICH and the number of tracks used during the MER' phase. Chi-square statistics were used to test for a difference between nominal variables, while Fisher exact test was employed when one or more cells in the contingency table had counts less than 5.

Multiple logistic regression analysis was chosen to predict the probability of developing seizures and ICH given specific predictor variables (i.e., age, number of trajectories, presence of perielectrode brain edema, different lead models). The full model was confronted with an intercept model only by means of chi-square test. For every predictor, standardized logistic regression coefficients, p values and odds ratios (with 95% CI) were calculated. Multicollinearity diagnostics was also carried out which excluded abnormal levels of variance inflation factors. Kaplan-Meier curves were performed to analyze the cumulative proportions of hardware-related complications throughout time and the log-rank test was used to further compare the specific survival functions of different IPGs. All P-values reported are two-tailed and a $P<0.05$ was considered statistically significant. Computations and graphs were made using SPSS (IBM Corp. Release, IBM SPSS Statistics for macOS, Version 26.0).

Results

Nine hundred ninety-three leads were implanted in 517 procedures, 832 of which were positioned in the STN, 158 in the GPi, 2 in the Zin, and 1 in the Vim. In 126 cases (24.4%), directional leads were implanted. Of the surgeries performed, 477 were first implants (92.3%) and 20 (3.9%) were second implants, while 20 (3.9%) were carried out as rescue therapies.

Patients who underwent rescue therapy [37] DBS suffered from a higher rate of adverse events compared to those who received first implants or reimplants (25% vs. 8.6% vs. 0% respectively; $P= 0.026$, Fisher's exact test). While direct surgical mortality was 0%, overall mortality was 0.2%, due to a patient who suffered from an aspiration pneumonia 1 week after surgery while still in hospital, and who later developed lung infection and respiratory failure (although it is worth reporting that the patient presented dysphagia preoperatively). Surgical morbidity was 0.6% (1 patient with permanent hemiparesis, and 2 patients with aphasia and permanent hemiparesis due to intraparenchymal hemorrhage).

Procedure-related adverse events

Procedure-related adverse events are shown in Table 1, and were further subdivided into complications during surgery and complications occurred in the perioperative period. Moreover, the complications which were encountered more frequently (i.e., ICH, seizures, perielectrode brain edema, infections) are discussed in greater detail below.

There were 17 cases of (3.3%) intraoperative complications, namely we reported 5 episodes (1.0%) of intraoperative seizures, 1 episode of lead breakage (0.2%), 1 episode of bradycardia and hypotension (0.2%) that led to interruption of surgery, 1 intraparenchymal hemorrhage (0.2%), 4 lead misplacements which required intraoperative repositioning (0.8%), one episode of stereotactic head frame displacement (0.2%), and four episodes of severe agitation (0.8%). In three cases (0.6%), surgery resulted in the inability to complete the procedure.

Thirteen patients (2.5%) presented with severe behavioral symptoms after surgery, which regressed in a few weeks. Other isolated complications include one case of pulmonary embolism about 3 weeks after surgery and another of cerebrospinal fluid leakage at the calvarium 1 week after

Table 1 Intraoperative and post-surgical DBS complications. *ICH*, intracerebral hemorrhages

Complications	n. (%)
Mortality	1 (0.2%)
Seizures	17 (3.3%)
ICH	13 (2.5%)
Symptomatic	8 (1.5%)
Non symptomatic	5 (1%)
Postoperative brain edema	187 (36.2%)
Symptomatic	14 (2.7%)
Non symptomatic	173 (33.5%)
Misplaced electrode*	16 (3.1%)
Lead infections	10 (1.9%)
Cognitive/psychiatric symptoms	13 (2.5%)
Hydrocephalus	1 (0.2%)
Head frame displacement	1 (0.2%)
Bradycardia and hypotension	1 (0.2%)
Lead breakage	1 (0.2%)
Cerebral Spinal Fluid Leakage	1 (0.2%)

*Misplaced electrodes include both intraoperative (which were repositioned during the same procedure) and post-procedural misplacements

surgery that resolved after compressive dressing of the wound.

ICH

A total of 13 (2.5%) cases of intracerebral hemorrhage were encountered throughout our cohort, 12 of which occurred in the perioperative period. Eight patients (1.5%) developed neurological deficits due to intraparenchymal bleeding. Those patients were treated according to the size of hematoma and/or the presence of intraventricular bleeding: 2 patients required hematoma evacuation; another patient required EVD placement for intraventricular hemorrhage. Of those discussed, 4 patients had a complete recovery from the neurological deficit with mild or no disability. However, 3 patients (0.6%) had permanent hemiparesis and aphasia due to the hemorrhage.

No association was found between ICH and the number of tracks utilized for MER using Spearman's rank correlation (ρ= −0.007, *P*= 0.875). Likewise, other parameters such as age (*P*= 0.979, Independent-Mann-Whitney *U* Test) and the specific target (STN vs. GPi, *P*= 0.445, Fisher's exact test) also failed to account for significant differences between patients who suffered from post-surgical ICH and those who did not.

Table 2 Distribution of cases of post-surgical perielectrode edema using 3, 4, and 5 trajectories during MER

	3 tracks	4 tracks	5 tracks
Perielectrode edema	158 (36.8%)	30 (37%)	0 (0%)
No perielectrode edema	271 (63.3%)	51 (63%)	6 (100%)
Total	429 (100%)	81 (100%)	6 (100%)

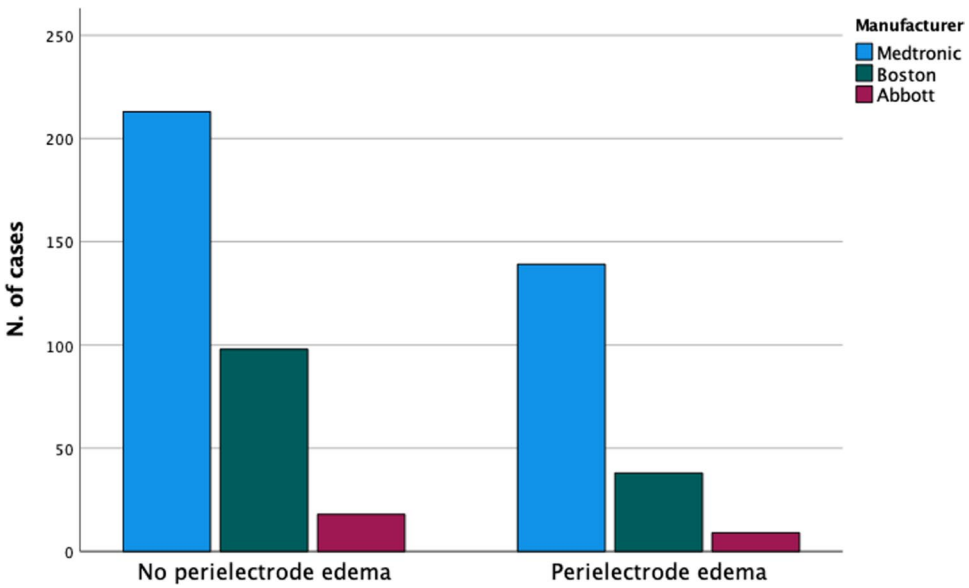
Perielectrode brain edema

Perielectrode brain edema (which was diagnosed with a postoperative 1.5 T MRI or by means of a CT scan) was found in 187 cases (36.2%), 14 of whom (2.7%) were symptomatic. No association was found between the number of tracks used and the incidence of brain edema using Chi-square test ($X^2(2)$= 3.481, *P*= 0.175) (Table 2).

Interestingly, when comparing the rates of edema between the three manufacturers (Medtronic, Boston Scientific, and Abbott), a significant difference was obtained when confronting Medtronic to Boston Scientific, with the former exhibiting a higher rate of events ($X^2(1)$= 5.927, *P*= 0.015; Graph 1); conversely, significance was not met when Abbott's electrodes were compared to both Medtronic's ($X^2(1)$= 0.399, *P*= 0.528) and Boston Scientific's ($X^2(1)$= 0.319, *P*= 0.572), although these findings are likely affected by the limited number of cases in the Abbott category (Graph 1).

Seizures

We encountered 17 cases (3.3%) of intraoperative or postoperative episodes of seizures. Using multiple logistic regression analysis (Table 3), two parameters were found to be significant predictors of this complication: occurrence of perielectrode edema and age. While the presence of the former positively correlated with the onset of seizures (B= 1.116, OR= 3.053, 95% CI OR= 1.017–9.169, *P*= 0.047), surprisingly the latter vice versa displayed a weak negative correlation (B= −0.066, OR= 0.936, 95% CI OR= 0.882–0.994, *P*= 0.032) which implies that younger individuals were more at risk for this type of complication. Importantly, none of the 17 patients



Graph 1 Distribution of cases of perielectrode brain edema among patients implanted with Medtronic', Boston Scientific' and Abbott' electrodes

Table 3 Logistic regression predictor variables for onset of post-surgical seizures. *ICH*, intracerebral hemorrhage. Electrode's manufacturer brands were Medtronic, Boston Scientific, and Abbott

Parameter	Beta weight	P	OR	Lower 95% CI for OR	Upper 95% CI for OR
Electrode's Manufacturer		0.913			
Age	−0.066	0.032	0.936	0.882	0.994
Tracks used	0.198	0.805	1.219	0.254	5.852
Target*	1.090	0.060	2.975	0.954	9.275
Perielectrode edema	1.116	0.047	3.053	1.017	9.169
ICH	1.317	0.046	3.731	0.635	21.919

*Targets included in this computation are STN and GPi. Two cases of VIM and ZIN were excluded because of their neglectable frequency (n= 1)

suffered from preoperative seizure disorders or from other neurological diseases besides Parkinson's disease.

Infections

We reported a total of 10 cases (1.9%) of system infections during the follow-up period. None of these patients showed significant comorbidities. We encountered only one case of frank cerebral abscess (0.2%), while the remaining cases of infections involved the surgical wounds (either cranial or concerning the IPG) with no evidence of intracranial extension.

All patients underwent removal of the electrode and were started on an antibiotic therapy. Five cases (1%) of major infections that started from the IPG and rapidly extended along the extension wires were seen. In these patients, both the IPG and the extension wires were removed to achieve infection' healing and to prevent intracranial dissemination of the infection. Antibiotic therapy was maintained for 3 weeks. Two patients were reoperated, with a successful reprise of STN-DBS. The only case of intracranial abscess was subsequently treated with surgical removal of the electrode and stereotactic drainage of the abscess.

STN vs. GPi

Considering the two most utilized targets (STN and GPi), no significant differences were found in rates of complications for what concerns ICH, brain edema, infections, and cases of electrode misplacements, but the GPi group did however report a significantly higher proportion of seizures compared to the STN as shown in Table 3 (7.3% vs. 2.5%, P= 0.039, Fisher's exact test). In line with these results, also the rate of electrodes requiring explanation (42 cases, 8.1%) was statistically the same among the two targets ($X^2(1)$= 2.633, P= 0.125) (Table 4).

Table 4 Distribution of peri- and post-surgical complications between the two most utilized targets (STN and GPi). Two cases of VIM and Zin stimulation have been omitted from the computation because of their neglectable frequency (n= 1)

Complication	STN (n= 433)	GPi (n= 82)	P
ICH (n, %)	10 (2.3%)	3 (3.7%)	0.445#
Seizures (n, %)	11 (2.5%)	6 (7.3%)	0.039#
Perielectrode brain edema (n, %)	160 (37.0%)	27 (32.9%)	0.532*
Infections (n, %)	9 (2.1%)	1 (1.2%)	1.0#
Electrode misplacements (n, %)	15 (3.5%)	1 (1.2%)	0.488#

#Comparison made between categorical variables using Fisher's exact test

*Comparison made between categorical variables using Chi-square test

Table 5 Complications which required surgical revision for electrode explantation. ICH, intracerebral hemorrhage. Hardware-related dysfunctions include wound dehiscence, impedances issues, extension wire breakage, lead fracture/malfunction

Explanted electrodes	Count (%)
Wound dehiscence (n, %)	16 (3.1%)
Infections (n, %)	10 (1.9%)
Electrode misplacement (n, %)	7 (1.3%)
Lead migration (n, %)	4 (0.8%)
No clinical response (n, %)	2 (0.4%)
Hardware-related dysfunctions* (n, %)	2 (0.4%)
ICH (n, %)	1 (0.2%)
Total (n, %)	42 (8.1%)

Explanted electrodes

Overall, 42 patients explanted one (or both) electrodes after DBS treatment (Table 5). Most frequent complications necessitating lead removal included 16 cases (3.1%) of wound dehiscences, 10 infections (1.9%), 7 electrode misplacements (1.3%), and 4 lead migrations (0.8%; Table 5).

Hardware adverse events

Overall, 63 implants (12.2%) have been surgically revised because of hardware-related complications (Table 6). In 12 of them (2.3%), more than one hardware-related problem occurred.

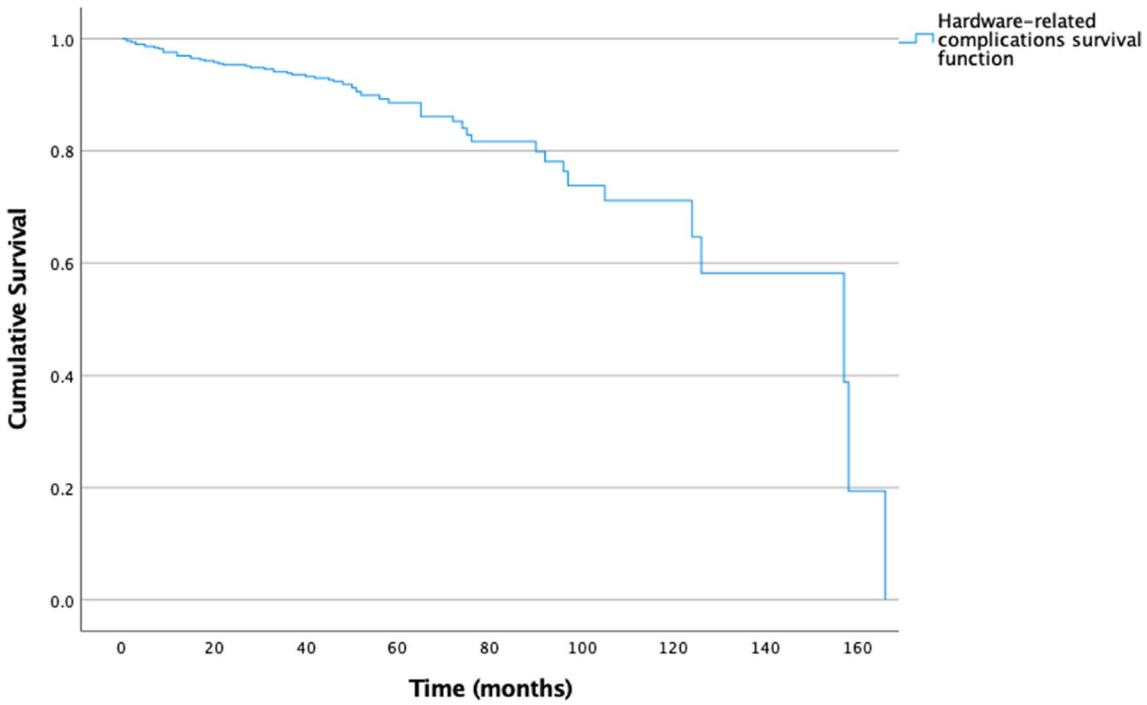
In 37 cases (7.2%), a wound revision was carried out due to skin erosion. Eleven (2.1%) of these patients necessitated a second operation, 3 (0.6%) a third operation, and 4 (0.8%) a fourth operation. Only 1 patient (0.2%) underwent more than 3 wound revisions; nevertheless, also in this specific case, the system was not removed. Lead extensions were revised in 31 (6%) cases due to high impedances (n= 19, 3.7%) or breakage/disconnection (n= 12, 2.3%) of one or more extensions (Table 6).

After performing survival analysis (Graph 2), cumulative proportions of cases free from hardware-related complications at 2, 5, and 10 years from implantation were found to be 91.7%, 86.2%, and 65.1% respectively.

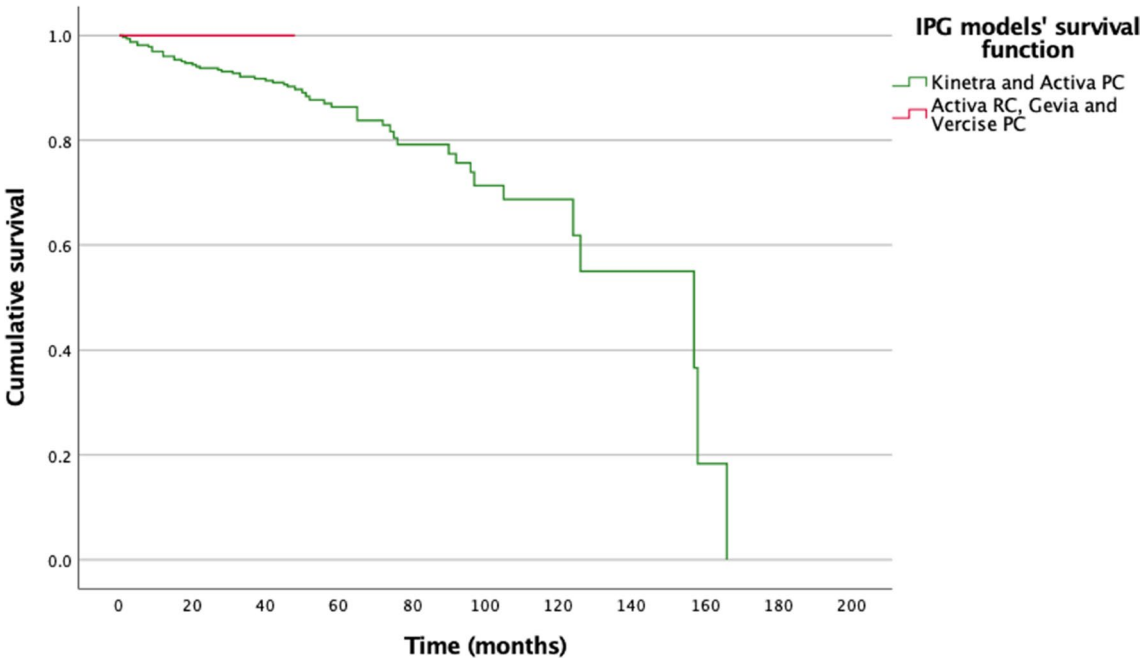
Overall, hardware-related complications directly linked to the IPG occurred in 34 cases (6.6%) of which 6 wound dehiscences. All the IPG were from Medtronic, namely Kinetra or Activa PC. No complications of Boston Scientific's IPGs or Medtronic Activa RCs were reported; this difference was statistically significant (P< 0.001, Fisher's exact test). Survival analysis further confirmed such finding by comparing the curves related to the first hardware complication of the IPG models with larger volumes and profiles (Kinetra and Activa PC) with their counterparts characterized by smaller designs (Activa RC, Gevia and Vercise PC) with a P= 0.004 ($X^2(1)$= 8.139; log rank test; Graph 3). To analyze the learning-curve effect, we divided our cohort in three tertiles according to the time of implantation, from those operated between 2006 and 2012, those between years 2012 and 2017, and the most recent ones performed between 2017 and 2021. Surprisingly survival analysis did not yield any significant difference in the occurrence throughout time of hardware related complications ($X^2(1)$= 2.286; P= 0.131; log rank test).

Table 6 Hardware-related complications. IPG, internal pulse generator

Hardware-related complication	Count (%)
Wound dehiscence	37 (7.2%)
Single site	30 (5.8%)
Multiple sites	7 (1.4%)
Impedances issues	19 (3.7%)
Extension wire breakage	12 (2.3%)
IPG migration	4 (0.8%)
Lead migration/fracture/malfunction	3 (0.6%)
Total	63 (12.2%)



Graph 2 Survival curve representing the occurrence of the first hardware-related complications (wound dehiscence, impedances issues, extension wire breakage, IPG migration, lead migration/fracture/malfunction) for which a surgical revision was needed. IPG, Internal Pulse Generator



Graph 3 Survival curves representing the occurrence of the first hardware-related complications (wound dehiscence, impedances issues, extension wire breakage, IPG migration, lead migration/fracture/malfunction) of the IPG models with large volumes and profiles (Kinetra and Activa PC; green line) and those with smaller designs (Activa RC, Gevia and Vercise PC; red line). IPG, internal pulse generator

Discussion

DBS is a minimally invasive procedure believed to be reversible and adaptable. However, it remains a surgical procedure, and, therefore, prone to complications. Some of them may be disabling or even life-threatening. Other, especially those related to the hardware are not severe but may reduce patients' quality of life and may represent a relevant cost. Since DBS is in unceasing expansion, to correctly assess the risk-to-benefit ratio is pivotal. Here, we present a consecutive case series of 517 cases of Deep Brain Stimulation for Parkinson's disease operated in the same center by the same neurosurgeon (DS).

Our observed rate of DBS-related ICH (2.5%) was near the lower limit of the range of percentages reported in literature (1.0–25.0%) [5, 11, 15]. Multiple factors may be possible linked to an augmented risk of ICH. According to our experience and to literature, MER do not seem to affect the risk of ICH. Nonetheless, other authors suggest that the number of MER tracks used during DBS seems to correlate directly with the same risk. Binder et al. 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 [6]. Our case series (which is composed by a larger sample) does not confirm such theory: in fact, no significant difference was found in the rates of ICH when using 3 vs. 4 vs. 5 MER tracks. We progressively diminished the number of MER tracks avoiding those more posterior for safety reasons.

Nonetheless, due to the advance of preoperative imaging and target selection, intraoperative imaging (O-Arm, Airo), the experience of the neurosurgeon, and the introduction of directional leads, we reduced the number of microelectrodes per single side, from 5 to 3.

Although not considered in our paper due to limited number of patients suffering from hypertension at the time of DBS procedure, arterial hypertension has been demonstrated to carry a convincing association with hemorrhage. Hypertension was a statistically significant factor in 5 studies [17, 45, 52, 56, 57]. One study also reported that the combination of MER and hypertension significantly increased the incidence of bleeding but that when MER were not employed no additional risk of hemorrhage was detected in patients with hypertension [17].

As published before by our center, venous infarction is another major concern during stereotactic lead positioning. One of our patients developed a major venous hemorrhagic infarct following coagulation of a superficial convexity vein: the patient developed an important venous hemorrhagic infarct which required an urgent surgical intervention of hematoma evacuation [38, 58].

Reducing the number of brain penetration per procedure is pivotal in reducing the risk of hemorrhages; therefore, improving the accuracy of initial image-guided targeting should be considered a key point in presurgical planning. Indeed, a clear association between ventricular involvement, decreased targeting accuracy, and requirement for multiple brain passes has also been demonstrated [10, 16].

Trajectory is fundamental in minimizing the risks. The formation of pneumocephalus during the procedure has been correlated with brain shift and increased target inaccuracy [18, 21]. Certain factors as brain atrophy (as seen in elderly patients), arterial hypertension, and supine position have been correlated with the formation of pneumocephalus [3, 25].

In a similar manner to ICH, also the rate of postoperative perielectrode brain edema was not affected by the number of tracks used. Conversely, our research reported different rates of brain edema between the three different manufacturers of electrodes, Medtronic displaying the highest incidence (39.5%) compared to Boston Scientific (27.9%) and Abbott (33%). Although statistical significance was met only when comparing Medtronic to Boston Scientific, the sample size in the Abbott group may be too limited to draw conclusions on this third category. Because the selection of the specific electrode type for every case of DBS can be considered random with regard to patients' clinical features (making this analysis robust to selection bias), this difference could be ascribable to the specific material composition of the electrodes. Nevertheless, we cannot exclude the influence of other unknown confounding factors especially considering that this is a first-ever finding. Although the percentage of patients with symptomatic brain edema was low (2.7%) and moreover this complication was always self-limiting, to our knowledge it is not known whether such tissue reaction may result in accelerated glial scar formation around the leads [51]. Perielectrode brain edema is thought to be the result of a foreign-body response to neural implants, leading to activation of microglia, subsequent release of proinflammatory cytokines, recruitment of blood-borne monocytes and neutrophils, and proliferation and hypertrophy of astrocytes which may culminate in electrode encapsulation [24, 32, 53]. Such phenomenon is thought to alter impedances, reduce the number of neurons stimulated, and diminish the effective volume of tissue activated [24, 29, 36, 44]. Although the role of perielectrode gliosis in DBS is still a matter of debate among investigators, and a recent retrospective study reported no difference in improvement in motor scores at 1-year follow-up between patients with symptomatic perielectrode edema and individuals who did not develop brain edema after DBS, it may be preferable to aim to reduce the volume of inflammation and glial activation, therefore keeping postsurgical brain-edema to a minimum [51].

Because we are the first to report a significant difference in the rate of perielectrode brain edema among different lead models, we believe that this finding should first be confirmed by other investigators before examining more in depth the material composition of the leads in order to produce electrodes with the highest neural biocompatibility profile.

1.9% of our implants developed infections in the postoperative course with only a single case of intracranial abscess. Such frequency is undoubtedly lower from that reported in literature. A recent meta-analysis found a summary prevalence of 5% (95% CI: 4–6%) of infections, with higher rates for specific indications such as epilepsy, dystonia, and Tourette's syndrome [23]. Conversely, our study includes only patients affected by Parkinson's disease which might partly explain such discrepancy. Nonetheless, we cannot exclude that outcome reporting bias may have influenced the rate. While intracranial infections can be easily identified on MRI, distinguishing a wound dehiscence from an infection is not always clear-cut. The criteria we applied to recognize a surgical site infection were in line with those of the CDC, which briefly include the isolation of organisms from an aseptically obtained culture, and the presence of local and/or systemic signs and symptoms of infection (purulent discharge, swelling, redness, tenderness, warmth, and fever) [35]. Nonetheless, it is also possible that some of the cases of wound dehiscences we encountered were caused be underlying infections which went undiagnosed. Because antibiotic therapy was administrated after surgical revision in cases of both wound dehiscence and surgical site infection, the distinction between the two is more challenging.

Although patients treated with GPi targeting exhibited a significantly higher rate of seizures compared to STN, such finding was not confirmed by multivariate analysis. The rate of peri- and postoperative seizures found in our series ($n = 17$; 3.3%) falls within the higher limit of the 95% CI described in a systematic review of Coley et al. which reported 42 seizures out of 1555 cases of DBS (2.7%; 95% CI: 1.6–3.3%) [12]. Other more recent retrospective series reported similar, or even slightly higher, frequencies [2, 43]. Importantly, after carefully reviewing the 17 cases of seizures in our series, we found that none of the patients suffered from epileptic syndromes or from other neurological disorders other than Parkinson's disease prior to these events. Similarly, a retrospective series analyzing the occurrence of seizures among 645 patients undergoing DBS implants did not find any significant association between the onset of such seizures and the presence of a preexisting epileptic disorder [2]. Our multivariate analysis instead reported a significant positive correlation with postoperative

perielectrode brain edema. Other authors also found a significant association between postoperative seizures and abnormal postoperative imaging (either edema, ischemia, or hemorrhage) suggesting that seizures are more likely a consequence of vascular events or mechanical trauma (due to the insertion of the electrodes) rather than a condition which arises from biological predisposing factors [12, 40, 43, 47, 55]. Notably, there was a significant association between ICH and seizures in our series (both intraoperative and postoperative). Such cases are likely to be a consequence of intracerebral bleeding; their onset therefore must prompt physicians to perform an urgent cerebral CT scan.

The only significant preoperative predictive factor which emerged from our multivariate analysis was age. Curiously, younger individuals appeared to be at higher risk for seizures. Atchley et al. (who also found this inverse association in their series) postulate that this phenomenon may be due to the lower tolerance for perielectrode edema or hemorrhage among younger individuals [2, 40, 47].

In 12.2% of the implants, hardware-related issues occurred; for these complications, surgical revision was needed. The most encountered types were wound dehiscence (skin erosions), accounting for 7.2%, followed by impedances issues (3.7%). The pathogenesis of the former is likely multifactorial and apart from the hardware per se, other factors are likely implicated including the experience of the surgical team, the surgical technique, and specific patient-related risk factors. Several reports, for example, have underlined the importance of the learning curve in reducing these complications [6; 9; 42]. Curiously, in our study, survival analysis did not yield any significant differences between patients operated in the oldest tertile (2006–2012), those in the intermediate (2012-2017) and those in the most recent (2017-2021). However, because all surgeries were performed by the same surgeon (DS) who already had an extensive experience in the field of deep brain stimulation (i.e., more than 10 years) when the first cases of the study were performed, it is likely that an advanced level of experience may have blunted the learning curve effect. Nevertheless, the refinement of the surgical technique is believed to influence rates of wound dehiscences [59]. Tension-free closures, preservation of the vascular supply, and adequacy of the subcutaneous tissue are some technical aspects which may help to prevent skin erosions [59]. Constantoyannis et al. [13] also reported a minor rate of wound dehiscences using curved incisions rather that straight. Regarding the implantation of the IPG in particular, Sarica et al. [46] suggested the use of potential surgical strategies to prevent skin erosions such as avoiding small-size pouches, performing deeper implantations and proper fixation with the use of anchoring sutures to avoid intra-pocket mobility. Together with the surgical technique, patient-specific characteristics are also implicated: a recent meta-analysis, for example, has highlighted an increased frequency of wound complications among smokers which is likely related to lower tissue oxygenation, blood flow, and impaired reparative tissue functions among these individuals [22, 23]. Other risk factors such as anemia, diabetes mellitus, poor nutrition, and thickness of the overlying skin have also been (although inconsistently) linked to wound dehiscences [5, 9].

It is nonetheless possible that certain features (e.g., volume, material composition) of the implants may come into play as well. For example, the significant difference which we found in the number of wound dehiscences between IPGs with larger volumes and profiles (Activa PC and Kinetra) compared to their smaller versions (Boston Scientific IPGs and Activa RC) may suggest the need in the future to reduce prosthetic's dimensions as possible to reduce skin erosions [8]. In this regard, a previous report had already revealed a higher rate of surgical-related adverse events in patient implanted with the wider and heavier Kinetra's IPG compared to Soletra's [42]. Moreover, in our opinion, round edges should be preferred to quadrangular designs.

Although usually not life-threatening, hardware-related issues increase the economic burden associated with DBS and cause patient discomfort, moreover negatively impacting the willingness of patients to opt for brain stimulation vs. conservative therapy.

A solution may be represented by the development of novel instruments and by means of capsulotomy during IPG replacement as demonstrated in Literature [49].

Considering patient's satisfaction over DBS treatment, it is important to remember that complications are not limited to those associated with the surgical procedure, but also extend to stimulation-related adverse effects. Because the latter are target-specific and at least partially reversible by adjusting stimulation settings, we choose not to include them in the scope of our study. Regarding PD, the most described stimulation-related complications are increased dyskinesia and blepharospasm, manic episodes, confusion, weight gain, dysphonia, dysarthria, diplopia, limb numbness, and tonic muscle pulling [11, 26, 34]. Nevertheless, they represent an important aspect of the adverse-effect profile related to brain stimulation which should not be ignored.

Accurately reporting complications related to DBS is an essential step to deal with expectations for clinicians and patients, and to promote the constant improvement of the safety profile of the procedure. Because DBS is a rapidly expanding field of research, and the number of patients treated with this therapy is constantly rising, it is imperative to maximize both the precision (ideally aiming to an error close to zero) and the safety profile of the procedure by lowering the number of the associated complications.

Although our study confirms that overall DBS surgery has to be considered a safe procedure in terms of morbidity and mortality, the relatively high number of hardware-related complications still remains an active concern to be addressed in the future; moreover, research should also continue to further improve the rates of complications as postoperative perielectrode brain edema or cerebral hemorrhages.

Strengths and limitations

With 517 cases of DBS our study is one of the largest to our knowledge. Moreover, the mean follow-up of 4.68 ± 2.86 years provides a complete picture of both short- and long-term complications. Nonetheless some limitations must be noted. First, our study is representative of patients with Parkinson's disease treated with DBS either with STN, or GPi targeting. Patients affected by other diseases and/or in whom different neural targets are selected are likely to present different complications' profiles. Therefore, caution must be exerted when generalizing these results to different DBS patients' populations. Secondly, due to the retrospective nature of the study, there is a possibility some complications may be underreported (as the case of infections as previously noted), or overreported due to classification, hindsight, and recall bias.

Conclusions

With a cumulative rate lower than 1%, comprehensive of both morbidity and mortality, DBS of both STN and GPi has to be considered a safe procedure. Nonetheless, the rate of hardware-related complications (12.2%) is still an open issue, especially for what concerns wound dehiscence. The refinement of surgical techniques together with smaller and lighter novel implant designs could aid surgeons in lowering the rates of these complications. Moreover, more data will be needed to confirm the higher rate of perielectrode brain edema found in patients implanted with Medtronic's devices compared to Boston's. Although the long-term effects of this complication are still uncertain, it may be preferable to aim for implants with the highest neurocompatible profile possible. Perielectrode brain edema is also associated with a higher likelihood of postoperative seizures. Lastly, our study confirms that the number of tracks used does not significantly influence chances of ICH and brain edema.

Author contribution All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Domenico Servello, Tommaso Galbiati, and Guglielmo Iess. The first draft of the manuscript was written by Domenico Servello and Tommaso Galbiati and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability Not applicable.

Code availability Not applicable.

Declarations

Ethics approval The work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. All the patients signed a written informed consent for the specific procedure.

Consent to participate Not applicable.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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Comments The present article discusses the relevant topic of possible complications in DBS surgery. I congratulate the authors on this paper, on their courage to critically evaluate and discuss their own interventions and results, and for making the readership aware of this important topic. An interesting and new aspect is the occurrence of edema around the electrodes and potential differences between the manufacturers and lead models, an issue to which more attention should certainly be paid in the future. As we know, problems, complications, and side-effects can in principle be caused by the procedures itself, by the implants inserted, or by the subsequent stimulations. Thus, all parties concerned, the neurosurgeons who perform the operations, the manufacturers of the hardware and software, and the neurologists providing further treatment are called upon to get involved to improve more and more the quality of DBS therapy and to further reduce the associated risks and complications.

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