Changing of the guard: reducing infection when replacing neural pacemakers

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OBJECTIVE Infection of deep brain stimulation (DBS) hardware has a significant impact on patient morbidity. Previous experience suggests that infection rates appear to be higher after implantable pulse generator (IPG) replacement surgery than after the de novo DBS procedure. In this study the authors examine the effect of a change in practice during DBS IPG replacements at their institution.

METHODS Starting in January 2012, patient screening for methicillin-resistant *Staphylococcus aureus* (MRSA) and, where necessary, eradication was performed prior to elective DBS IPG change. Moreover, topical vancomycin was placed in the IPG pocket during surgery. The authors then prospectively examined the infection rate in patients undergoing DBS IPG replacement at their center over a 3-year period with at least 9 months of follow-up.

RESULTS The total incidence of infection in this prospective consecutive series of 101 IPG replacement procedures was 0%, with a mean follow-up duration of 24 ± 11 months. This was significantly lower than the authors' previously published historical control group, prior to implementing the change in practice, where the infection rate for IPG replacement was 8.5% (8/94 procedures; $p = 0.003$).

CONCLUSIONS This study suggests that a change in clinical practice can significantly lower infection rates in patients undergoing DBS IPG replacement. These simple measures can minimize unnecessary surgery, loss of benefit from chronic stimulation, and costly hardware replacement, further improving the cost efficacy of DBS therapies.

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KEY WORDS deep brain stimulation; implantable pulse generator; infection; Parkinson's disease; reoperation; antibiotic; vancomycin; functional neurosurgery

DEEP brain stimulation (DBS) was popularized by the Grenoble group² and surpassed stereotactic ablation as the predominant treatment in functional neurosurgery at the end of the last millennium. DBS is now an established treatment for a number of movement disorders including Parkinson's disease, dystonia, and tremor. This has raised interest in the possible use of DBS for severe and unremitting psychiatric disorders including obsessive-compulsive disorder and depression.³¹

Despite the surge in popularity of DBS only a small number of publications have specifically analyzed the complications of DBS surgery,^{3,4,6,15,32,40,41} and even fewer have

assessed interventions that can reduce the rate of adverse events.^{3,14,24,26,28,37,46} Reported infection rates vary between centers from 0% to 22%.^{7,42} Our group recently published data demonstrating that infection rates after implantable pulse generator (IPG) replacement are significantly higher when compared with other types of DBS-related surgery.³² Other authors have reported similar trends.³ However, the overall picture is far from clear, as other groups reported infection rates similar to de novo surgery.^{4,36}

Miller and colleagues previously reported a significant improvement in hardware-related infection in all stereotactic and functional neurosurgical procedures with

ABBREVIATIONS DBS = deep brain stimulation; IPG = implantable pulse generator; MRSA = methicillin-resistant *Staphylococcus aureus*.

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the use of topical antibiotics.²⁸ Moreover, it is well documented that colonization with *Staphylococcus aureus* is an independent risk factor for the development of post-surgical infection,⁴⁴ and this risk may be as high as 33%.²⁹ Therefore, since January 2012 we adapted our surgical procedure with the aim of reducing the rate of infection after IPG replacement surgery. Together with our local infection control team we introduced the use of methicillin-resistant *S. aureus* (MRSA) screening and eradication as well as an intraoperative topical vancomycin wash during IPG replacement. The aim of this prospective study was to assess whether this change in practice made a significant impact on infection rates after IPG replacement surgery when compared with historical controls.

Methods

Surgical reports and clinical notes were reviewed in all 171 patients (89 men and 82 women) who underwent IPG replacement surgery at the National Hospital of Neurology and Neurosurgery, Queen Square, London, from November 2002 until December 2014. Prior to January 2012 all data collected were retrospective. From January 2012 until December 2014 all patients undergoing IPG replacement surgery were prospectively followed up.

Baseline patient characteristics (age at surgery, sex, diagnosis, brain target) as well as details of the operation performed were collected for each patient. Before January 1, 2012, the IPG pocket was vigorously washed with copious saline. After this date all patients underwent MRSA screening and eradication where appropriate prior to surgery, and at surgery the IPG pocket was instilled with a vancomycin wash prior to closure (further details below). Patients were grouped into a historical “control” group and a “prospective” group following this change in practice. All patients had a minimum follow-up duration of 9 months.

Information on any DBS-related infection, including type, site, and microbiological diagnosis, was collected for all patients with infection. The definition of recorded infection is the same as in our previous study.³² Only infections in direct relation to the hardware were considered. Infections were defined if any of the following were present: 1) clinical suspicion of an infection (i.e., redness, swelling, warmth, or fluid surrounding any of the DBS components beyond that expected due to postsurgical inflammation, with either elevated temperature or inflammatory markers); 2) purulent exudates from the suspected site of infection; 3) microbiological evidence; and 4) skin erosion with any of the above. The infection rate was calculated as the number of infections per patient as well as the number of infections per procedure.

Microbial Screening and Eradication Protocol

All patients in the prospective group attended a preoperative assessment clinic where they underwent skin and nasal screening for MRSA colonization. All patients who had negative colonization results continued to surgery without eradication. Patients underwent MRSA eradication if they 1) had a positive MRSA colonization result, 2) were unable to attend preoperative assessment clinic, 3) were historically MRSA-colonization positive, or 4) were a

known MRSA carrier undergoing delayed elective surgery with or without previous eradication. All patients with delayed elective surgery underwent repeat MRSA screening (Fig. 1). Table 1 lists details of the eradication protocol.

Replacement of IPG

Patients received a single dose of 1.5 g of intravenous cefuroxime or a single dose of 500 mg of intravenous clarithromycin in cases of penicillin allergy at induction. If patients were MRSA-positive, 6 mg/kg of intravenous teicoplanin was added to the primary prophylaxis. With the patient under general or local anesthesia, the pocket of the IPG was opened via the old scar. If the scar was unsightly, the scar was excised together with an ellipse of skin. The old IPG was replaced with the new IPG placed in the fibrous pocket. When exchanging the old IPG for more bulky hardware (such as a Kinetra IPG being replaced with an Activa PC via a cable adapter [Medtronic]), the new hardware was sometimes placed in a deeper pocket, formed beneath the pectoralis major muscle via a muscle-splitting approach, especially when the overlying skin was deemed thin.

Before January 1, 2012, the pocket was washed with copious amounts of saline. After this date, a vancomycin/saline wash was used (20 ml of 1 mg/ml vancomycin solution). The wound was closed in layers with carefully buried absorbable sutures and interrupted nylon for skin closure. The patient received 3 further doses of 750 mg of intravenous cefuroxime at 8-hour intervals or the appropriate alternative if the patient was allergic to penicillin or positive for MRSA. Dressings were not removed unless they were heavily blood stained, and sutures were removed after 10–14 days. Patients were instructed to keep the wound dry until 24 hours after suture removal.

Statistical Analysis

An unpaired Student t-test was used to compare the ages of patients with and without infection, between groups, and the number of surgeons per operation. The infection rate between groups was compared with a Fisher exact test using a 2 × 2 contingency table. A p value < 0.05 was considered significant.

Results

Baseline Characteristics

One hundred seventy-one patients underwent a total of 195 IPG replacement procedures. Of those in the historical control group, 80 patients underwent 94 IPG replacement surgeries (mean age 48 ± 20 years old, 48% male). This included 15 procedures (16%) in which patients had 1 or more previous IPG replacement surgeries. In the “prospective” group, 91 patients underwent 101 IPG replacement surgeries (mean age 54 ± 15 years, 56% male) and included 24 procedures (23.8%) in which patients had 1 or more previous IPG replacement surgeries. There was no significant difference in sex distribution, primary indication for DBS surgery, brain target, or rates of diabetes between the 2 groups (Table 2).

Minimum follow-up duration was 9 months in both groups, with a mean follow-up duration of 24 ± 11 months

FIG. 1. Flow chart showing the new IPG replacement protocol. * See Table 1 for the MRSA eradication protocol.

in the prospective group and 73 ± 26 months in the control group ($p = 0.0001$). The number of surgeons involved was higher in the control than in the prospective group (1.8 vs 1.4 surgeons, respectively; $p = 0.0002$). Patients in the prospective group were older, had a smaller proportion of patients with dystonia and Parkinson's disease, and had undergone more previous IPG changes (Table 2).

Rate of MRSA Colonization in the Prospective Cohort

There were no confirmed MRSA colonizations within the prospective group. However, 4 patients underwent MRSA eradication: 3 who had historical MRSA colonization and 1 who failed to attend the MRSA screening (Fig. 1).

Postoperative Infections

In total, 8 postoperative infections occurred in 6 patients in the historical control group. This corresponds to a patient infection rate of 7.5% and a procedure infection rate of 8.5%. There were no infections in the prospective group, and this difference was statistically significant (p

$= 0.003$; Fig. 2). Information on patients with infection is detailed in brief in Table 3 and in more detail in our previous publication.³² The mean duration until infection in the control group was 3.1 ± 5.8 months. None of the infections were secondary to MRSA.

Reason for IPG Replacement

The most common reason for IPG replacement was depletion/near depletion of the IPG's battery in both groups. Replacement of the IPG after prior hardware removal because of infection was the indication in 12% of the historical control group compared with 0% in the prospective group ($p = 0.0002$; Table 4).

Adverse Events

There were no adverse events noted in relation to the use of topical vancomycin wash or microbial screening/eradication.

Patients With Previous DBS-Related Infections

The historical control group contained 1 patient (1/80,

TABLE 1. MRSA eradication protocol during IPG replacement*

Type of Wash	Antimicrobial	Frequency	Length of Time (days)
Body wash	Chlorhexadine gluconate 4%†	Once per day	6
Hair wash	Chlorhexadine gluconate 4%†	Every other day	5
Nasal	Mupirocin 2%	3 times per day	5

* Protocol schedule as follows: Day 1, body wash, hair wash, and nasal; Day 2, body wash and nasal; Day 3, body wash, hair wash, and nasal; Day 4, body wash and nasal; Day 5, body wash, hair wash, and nasal; and Surgery, body wash.

† Octenisan (Schülke) was used as a substitute if chlorhexadine gluconate 4% was contraindicated.

1.2%) with a previous DBS-related infection, and the prospective cohort contained 4 patients (4/91, 4.4%) who had previous infection of DBS hardware. This difference was not statistically significant.

Special Cases

Of the 6 patients with IPG infections in the historical group, 2 deserve further discussion. Patient 2 underwent surgery for tardive dystonia and suffered 3 infections after IPG replacement surgery and 4 in total. The initial infection affected the IPG alone and was managed by cutting of the cables below the cranial connector site and extraction of the cut cables and IPG. The subsequent infection occurred 2 months later and was associated with erosion of the distal end of the cut extension cable through the skin, and the cable stump was removed. Four weeks later a purulent spot over the left pericoronal wound was noted, and the patient was admitted to the hospital for removal of the leads. These were all considered separate infections as they occurred at different time points all related to the most recent surgery (IPG replacement). Three and a half months later the entire system was reimplanted, but the patient developed a subcutaneous infection around the IPG pocket that resulted in removal of the infected components, leaving the leads in place. Finally, new cables and an IPG were reinserted 4 months later. This patient suffered from Type II diabetes mellitus.

Patient 3 with severe dystonia and cachexia underwent IPG replacement due to near depletion of the battery and was discharged back to his nursing home. The patient presented to the hospital 17 months later with erosion of the IPG through the skin. On presentation no clinical signs of infection were present and an attempt was made to rescue the IPG by excising the wound margins and forming a new pocket. This was followed by development of a purulent infection.

Discussion

The use of an intraoperative vancomycin wash and microbial screening significantly reduced the rate of infection after IPG replacement surgery from a procedure infection rate of 8.5%, and patient infection rate of 7.5%, to 0%.

In 5 of 6 patients with infection in the historical control group, the causative organism of purulent infection was

TABLE 2. Baseline characteristics

Variable	Control	Prospective	p Value
No. of patients	80	91	—
No. of procedures	94	101	—
Mean age (SD)	48 (20)	54 (15)	0.018*
Male (%)	48	56	0.25
Mean follow-up in mos (SD)	73 (26)	24 (11)	0.0001*
Diabetes mellitus % (no.)	1 (1/80)	2 (2/91)	0.80
Mean no. of surgeons (SD)	1.8 (0.7)	1.4 (0.6)	0.0002*
Parkinson's disease (%)	54	45	0.23
Dystonia (%)	42	42	1.0
Other diagnosis (%)	3	14	0.02*
Subthalamic nucleus (%)	48	37	0.17
Globus pallidus internus (%)	49	57	0.29
Other targets (%)	4	6	0.73
Patients w/ previous infections (%)	1.2	4.4	0.37
No. w/ ≥1 previous IPG change	15	24	0.58
No. w/ ≥2 previous IPG changes	4	15	0.048*

* Statistically significant.

Staphylococcus species. The rate of skin colonization of *S. aureus* is more than 70% in patients with confirmed skin and soft-tissue infections.^{10,25} The most common causative organism responsible for hardware infection in DBS surgery is staphylococcal species.^{3,4,32} Importantly, despite proper skin disinfectant and draping during surgery, bacteria including coagulase-negative staphylococci and *Propionibacterium acnes* will begin to colonize the skin within 1 hour, with a marked bacterial colonization load at 2 hours.¹²

S. aureus is a common commensal species that affects up to two-thirds of healthy individuals throughout their lifetime.^{22,25} The skin provides a remarkably resistant barrier to infection by colonized bacteria due to a large extent on the production of antimicrobial proteins such as defensins and cathelicidins.³⁰ Skin breaches during surgery allow the spread of *S. aureus* within the skin and deeper tissue layers. MRSA infections can be more serious than methicillin-sensitive *S. aureus* infections due to their reduced sensitivity to commonly used antibiotics and result in worse clinical outcomes.⁴⁵

Within the National Health Service in England, Public Health England reports that the rate of MRSA bacteraemia¹⁶ and surgical site infections⁹ have fallen markedly over the last decade. The reason for this is unclear, but screening and subsequent isolation and eradication protocols are believed to be contributory.⁴³

Topical application of antibiotics produces far higher intrawound concentrations than would be possible via intravenous administration alone. This is especially true in patients undergoing IPG replacement surgery where the subcutaneous fibrous pocket has a reduced blood supply. The topical use of a variety of antibiotics has long been used effectively in treatment and prophylaxis of wound infection.^{5,33,35} Moreover, in neurosurgical shunt operations the use of a local antibiotic injected directly into the shunt

FIG. 2. Graph showing the percentage of patients and procedures with infections.

reduced the infection rate from 6% to 0.4% in a controlled trial of 802 shunt procedures.³⁴

Staphylococcus species are highly sensitive to vancomycin. Thus, the use of a local vancomycin wash into subcutaneous tissue is judicious in hardware implantation surgery. In this study the use of a vancomycin wash in more than 100 procedures with an average follow-up duration of 2 years has resulted in no infections. Importantly, there were no adverse events noted from the use of vancomycin wash.

Change in Antibiotic Regimen

Bhatia and colleagues³ changed the perioperative an-

tibiotic regimen from intravenous cefuroxime to intravenous vancomycin and gentamicin. This change reduced the overall infection rate and importantly reduced their rate of infection after IPG replacement surgery from 17.6% to 3.6%. While highlighting an important trend, this study was underpowered, and the outcome was not statistically significant. The causative organism in this original report was *Staphylococcus* species in two-thirds of the cases of IPG replacement. In the highly detailed review conducted by the authors, the causative organism of infection was *Staphylococcus* species in more than 50% of cases.

Miller et al.²⁸ meticulously collected information on all stereotactic and functional hardware procedures over a 5-year period. In total, 614 patients underwent a variety of procedures including DBS, spinal cord stimulator, peripheral nerve stimulator, and other device implantations. All patients were given perioperative cephalosporin or vancomycin. In the final 18 months of this study, all subcutaneous pockets were irrigated with neomycin/polymyxin as opposed to saline prior to skin closure. The overall rate of infection was reduced from 5.7% to 1.2% ($p < 0.05$) in the group with the antibiotic washout. The causative organism of infection was *Staphylococcus* species in 82% (23/28) of cases.

In other fields of surgery and neurosurgery involving implantable hardware the use of topical vancomycin has led to marked reductions in the rate of postoperative infections. The use of a topical vancomycin powder in instrumented spinal surgery in a prospectively followed cohort led to a reduction in postoperative infection rates from 12.5% to 0%,²³ a finding similar to our own.

Microbial Screening and Eradication

Colonization with *S. aureus* is an independent risk factor for the development of postoperative surgical site infections.^{21,44} In our study, information on MRSA carrier status was not available for all historical controls because routine screening was not conducted until January 2012. Moreover, MRSA was not cultured from any of our infected patients. Nevertheless, prior knowledge of MRSA status led to prophylactic decontamination in 3 patients within our prospective cohort. Although we suspect that

TABLE 3. Characteristics of patients in the historical control group who suffered infection following IPG replacement*

Case No.	Age (yrs)	Diagnosis	Time to Infection	Hardware Involved	Type of Infection	Culture Result
1	61	PD	2 wks	IPG	Suppurative	<i>S. aureus</i>
2	63	Dystonia	3 days	IPG	Suppurative	Coagulase-negative staphylococcus
	64	Dystonia	2 mos	Cable	Erosion through skin	
	64	Dystonia	4 mos	Electrode (scalp)	Purulent spot around lt frontal incision	
3	36	Dystonia	17 mos	IPG	Erosion of IPG through skin	<i>Candida albicans</i>
4	40	Dystonia	9 days	IPG, cable	Suppurative	Electrode tip: <i>S. epidermidis</i>
5	43	Dystonia	3 days	Cable, electrode (scalp & brain)	Suppurative, cerebral abscess	<i>S. aureus</i>
6	43	Dystonia	1 mo	IPG	Suppurative	<i>S. aureus</i>

PD = Parkinson's disease.

* All patients were male. The target for DBS was the globus pallidus internus, bilaterally. Hardware was removed in all patients.

TABLE 4. Reasons for IPG change

Reason	Control	Prospective	p Value
Depleted battery	80	93	0.17
Infection	11	0	0.0002
Malfunction	2	4	0.7
Discomfort	1	2	1.0
Other*	0	2*	0.5

* Other includes 1 patient who required more complex programming and a second patient who had a poor response to a new IPG so an old model was reimplanted.

the majority of the benefit observed in terms of reduced infection rates was due to the use of topical vancomycin, we cannot discount a contribution from the introduction of routine MRSA screening.

Diabetes Mellitus

It is noted in neurosurgery¹¹ and other fields of surgery²⁹ that diabetes is an independent risk factor for the development of postoperative surgical infections. Importantly, in relation to this study, patients with MRSA colonization who underwent cardiac surgery were more likely to develop postoperative infection if they had a confirmed preoperative diagnosis of diabetes.²¹

In our patient groups, the rate of diagnosed diabetes mellitus was low and similar between the two groups. This rate is similar to other published series of DBS patients.^{36,41} Due to the low number of diagnoses, we cannot comment on its significance as a contributory factor in the development of postoperative infections. However, a number of other DBS-related publications have noted that diabetes does not appear to be correlated with the development of postoperative infections.^{20,39,41}

Timing of Infection and Follow-Up

In this study, 6 (75%) of 8 IPG infections in the control group occurred within 2 months of surgery, 7 (88%) of 8 occurred within 6 months, and all infections occurred within 17 months of surgery. The mean follow-up duration of 24 months and minimum follow-up of 9 months in the prospective group may thus be considered adequate to determine the rate of postprocedural infections. Therefore, it is unlikely that the (inevitably) shorter duration of follow-up in the second group contributed to the lower rate of infection in any meaningful way. Other studies support the notion that the majority of postsurgical infections (roughly 80%) occur within the first few months of surgery with a smaller proportion, often not directly related to surgery, occurring at a later stage, usually up to 2 years after the procedure.^{3,4,32}

Number of Surgeons

The number of surgeons was higher in the control group on average by 0.4 surgeons over 101 procedures. This might have contributed to the higher infection rate within the control group, although this is uncertain. Other groups have noted that the number of individuals present in the operating room is related to a higher infection rate.³⁹

However, at our institution the consultant (attending) surgeon listed in the operative record and supervising the procedure does not always scrub for the procedure. Therefore, these numbers must be interpreted with caution, and it is not clear whether the number of scrubbed surgeons is a significant contributing factor.

Number of Previous IPG Replacement Surgeries

We postulated in our previous publication that the number of IPG replacement surgeries might be an independent risk factor for infection.³² Our reasoning was 2-fold: that the fibrous pocket around the IPG does not provide an adequate inflammatory response to infection, and the likely reduced penetrance of prophylactic intravenous antibiotics increases the likelihood of an infection. The number of pacemaker changes is a risk factor for infection when compared with de novo implantation in cardiac surgery.^{1,8,17,18} Furthermore, in hip replacement surgery the rate of infection is 18% higher after repeat revision when compared with de novo surgery.²⁷ A recent publication has confirmed an increasing infection rate in multiple DBS IPG changes.³⁸

In our prospective group, 15% of all surgeries occurred in patients who had 2 or more previous IPG replacements, and almost a quarter of all patients had at least 1 previous IPG change. This is to be compared with 4% ($p = 0.048$) and 16% ($p = \text{non-significant}$) of patients in our control group, respectively. Although the number of IPG changes is an independent risk factor for infection, our protocol appears to significantly negate this risk in IPG replacement surgery.

Study Limitations

Comparison of a prospective cohort with a historical control group may have produced potential confounding that contributed to the difference in infection rates. Nevertheless, our DBS service has always been alert to the importance of minimizing infection. No changes were made to the surgical procedure in the prospective group other than the addition of topical vancomycin wash. Surgical learning curves may also lead to higher early complication rates.¹³ However, a surgical learning curve may not be present when a relatively simple procedure is performed by an experienced surgeon.¹⁹ Indeed, the majority of infections in the historical control group did not occur in the early years of our DBS service.³² Moreover, the prospective group was older with more repeat IPG changes, both independent risk factors for infection. These factors suggest that a greater baseline risk for the prospective group was reversed by using topical vancomycin wash.

Conclusions

The use of topical vancomycin has significantly reduced the rate of infection after IPG replacement surgery. MRSA screening and eradication may also have contributed to the reduced infection rate. No adverse events were noted, and our protocol appears to have negated the increased risk of infection associated with multiple IPG changes. These simple measures prevented unnecessary surgery, loss of benefit from chronic stimulation, and costly hardware

replacement, further improving the cost efficacy of DBS therapies.

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Disclosures

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Author Contributions

Conception and design: Zrinzo, Pepper, Meliak, Hariz. Acquisition of data: Zrinzo, Pepper, Milabo, Candelario. Analysis and interpretation of data: Zrinzo, Pepper, Foltynie, Curtis. Drafting the article: Pepper, Hariz. Critically revising the article: Zrinzo, Pepper, Akram, Hyam, Foltynie, Limousin, Curtis, Hariz. Reviewed submitted version of manuscript: Zrinzo, Pepper, Akram, Hyam, Foltynie, Limousin, Curtis, Hariz. Approved the final version of the manuscript on behalf of all authors: Zrinzo. Statistical analysis: Zrinzo, Pepper. Administrative/technical/material support: Pepper. Study supervision: Zrinzo, Hariz.

Supplemental Information

Previous Presentations

An abstract (oral presentation) of this work was previously presented at the biennial congress of the World Society for Stereotactic and Functional Neurosurgery in September 2015 in Mumbai, India, and at the Society of British Neurological Surgeons Meeting in September 2015 in York, United Kingdom.

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