Deep Brain Electrode Externalization and Risk of Infection: A Systematic Review and Meta-Analysis

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BACKGROUND: When evaluating deep brain stimulation (DBS) for newer indications, patients may benefit from trial stimulation prior to permanent implantation or for investigatory purposes. Although several case series have evaluated infectious complications among DBS patients who underwent trials with external hardware, outcomes have been inconsistent.

OBJECTIVE: To determine whether a period of lead externalization is associated with an increased risk of infection.

METHODS: We conducted a Preferred Reporting Items for Systematic Reviews and Meta-Analyses compliant systematic review of all studies that included rates of infection for patients who were externalized prior to DBS implantation. A meta-analysis of proportions was performed to estimate the pooled proportion of infection across studies, and a meta-analysis of relative risks was conducted on those studies that included a control group of nonexternalized patients. Heterogeneity across studies was assessed via I^2 index.

RESULTS: Our search retrieved 23 articles, comprising 1354 patients who underwent lead externalization. The pooled proportion of infection was 6.9% (95% CI: 4.7%-9.5%), with a moderate to high level of heterogeneity between studies ($I^2 = 62.2\%$; 95% CI: 40.7-75.9; $P < .0001$). A total of 3 studies, comprising 212 externalized patients, included a control group. Rate of infection in externalized patients was 5.2% as compared to 6.0% in nonexternalized patients. However, meta-analysis was inadequately powered to determine whether there was indeed no difference in infection rate between the groups.

CONCLUSION: The rate of infection in patients with electrode externalization is comparable to that reported in the literature for DBS implantation without a trial period. Future studies are needed before this information can be confidently used in the clinical setting.

KEY WORDS: Adverse events, Complications, Deep brain stimulation, Externalization, Infection

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Deep brain stimulation (DBS) is an established therapeutic modality in the treatment of Parkinson disease (PD), essential tremor, and dystonia and is currently under investigation for numerous other conditions.[1] Despite its promise, the surgical implantation of DBS hardware is not without risk.[2] Hardware-related infection is among the most recognized complications after DBS, often leading to additional operations, removal of implanted hardware, extended hospitalization, and prolonged use of antibiotics.[3]

The incidence of DBS-related infection ranges from 1.5% to 22.2%.[4-21] This disparity may relate to several factors, including varying indications for DBS, antibiotic prophylaxis, follow-up time, study design, and other risk factors. It is unclear how much hardware (or lead) externalization contributes or exacerbates the risk of infection. Historically, electrode externalization has been utilized in a period between intracerebral lead implantation and internal pulse generator (IPG) placement, during which the electrodes are temporarily connected to extension leads for trial stimulation prior to

ABBREVIATIONS: DBS, deep brain stimulation; **EVDs,** external ventricular drains; **ICP,** intracranial pressure; **IPG,** internal pulse generator; **PD,** Parkinson disease; **PRISMA,** Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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TABLE 1. Sample Search Strategy for PubMed

Number	Search terms
1	Deep brain stimulation [mesh]
2	Infection
3	Erosion
4	Skin
5	2 or 3 or 4
6	1 and 5
7	Filters: Humans; English

permanent hardware internalization. Such a trial period may be particularly useful for conditions such as chronic pain syndromes, in which intraoperative testing for DBS efficacy may be difficult and unreliable. Furthermore, a period of trial stimulation allows for the acquisition of neurophysiological data, critical to guiding us in future research and development in the area of DBS.[22] The process of electrode externalization may enable opportunities to develop future therapeutic applications, including enhancing clinical efficacy and limiting the adverse effects of DBS therapy.

Although the potential benefits from lead externalization are appreciated, data regarding its safety are both limited and controversial. The purpose of this study was to perform a systematic review and meta-analysis to investigate whether lead externalization is associated with an increased risk of infection after DBS implantation. We believe the results of this study will allow medical providers to better understand the risks of this method, give patients the necessary information to make a more informed decision about their care and enable rationale trial design for scientific investigation.

METHODS

Search Strategy

This systemic review was performed in accordance with the criteria outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 guidelines.[23] No patient information was used in this article, so Institutional Review Board approval and patient consent were not required. A computerized search was conducted up to February 2020 on the PubMed and Web of Science online databases. The search strategy was based on the population, intervention, comparison, outcome framework and was developed using the following main subject terms: deep brain stimulation, infection, erosion, and skin (**Text**, **Supplemental Digital Content A**). A sample search strategy can be found in Table 1. The reference lists of the included studies were searched to obtain additional articles.

Study Selection

Studies were included if they met the following criteria: (1) human subjects, (2) English language, (3) included patients greater than 19 yr of age, (4) peer-reviewed original research with full-text available (single-subject case reports, reviews, systematic reviews, and meta-analyses were excluded), (5) included patients who were externalized prior to full DBS implantation, and (6) reported rates of infection with respect to those patients who were externalized. Studies were excluded if they did not meet all the inclusion criteria. Skin erosions were distinguished from infections and were not included in the infection count.

In the first phase, all studies were evaluated for eligibility based on the title and abstract. In the second phase, full-text articles were evaluated on meeting the inclusion criteria. Study selection and data extraction were independently performed in a standardized form by the first author, supervised by 2 independent reviewers.

Quality Assessment

Tools for assessing the quality of studies evaluating surgery and hardware-related complications, such as infection, are generally not available.[24] For this reason, the authors were unable to compare the methods of included studies using an established quality assessment standard. Nevertheless, factors related to internal validity were extracted for further assessment. Based on the analysis of levels of evidence,[25] 1 study was classified as level I,[26] 2 studies were classified as level III,[27,28] and the remaining 20 studies were classified as level IV.[11,22,29-46]

Data Extraction

Relevant information from each included article was extracted and presented in 2 tables containing the following items: (1) author and date of publication, (2) number of patients who underwent electrode externalization and were followed-up, (3) follow-up duration, (4) use of antibiotic prophylaxis, (5) indication for external trial stimulation, (6) duration of external trial stimulation, (7) study design, (8) the presence of a control group, (9) whether or not infection was defined (Table 2), (10) number of patients with infection, (11) infection rate, (12) DBS indication for those patients with infection, (13) time from DBS surgery to infection, (14) microbiology of infection, (15) site of infection, (16) management of infection, and (17) whether or not there was an increased risk of infection with externalization (Table 3).

Statistical Analysis

A meta-analysis of proportions was performed using MedCalc (MedCalc Software Ltd) version 19.0.5 in order to estimate the pooled proportion of infection across studies. MedCalc uses a Freeman-Tukey transformation[47] to calculate the weighted summary proportion under the fixed- and random-effects model.[48] Additionally, we used MedCalc to perform a meta-analysis of relative risk on the subgroup of studies that included a control group of nonexternalized patients. For this analysis, MedCalc uses the Mantel-Haenszel[49] method for calculating the weighted pooled relative risk under the fixed-effects model and then incorporates the heterogeneity statistic to calculate the summary relative risk under the random-effects model.[48] In order to assess the possible effects of study design (retrospective vs prospective) and duration of externalization (<7 d vs ≥ 7 d) on the rate of infection, we performed a meta-regression with the "metareg" command using Stata (StataCorp LLC) version 15.1. All other outcomes were assessed by descriptive statistical measures. A P value of $<.05$ was defined as statistically significant.

Because of potential heterogeneity across studies, we determined that a more conservative estimate of proportions was best representative of our study group, and therefore, the random-effects model was justified as the preferred model for our analyses.[50] Heterogeneity was assessed using the I^2 value. In accordance with the recommendation by Higgins et al,[51] I^2 values of 25%, 50%, and 75% may correspond with low, moderate, and high levels of heterogeneity, respectively.

TABLE 2. Study Characteristics of Studies Relating to Electrode Externalization and Infection

Author, year	No. externalized	Mean follow-up in months (range)	Antibiotic prophylaxis?	Indication (no. of patients)	Duration of externalization (days)	Study design	Nonexternalized control group?	Defined infection?
Franco, 2018[34]	4	6.0 (6.0)	INS	PWS (4)	5	P	No	No
Boccard, 2017[39]	24	38.9 (24-65)	INS	Pain (24)	7	R	No	No
Rosa, 2017[22]	105	12.0 (INS)	Yes	PD (105)	2-7	R	No	Yes
Lee, 2014[27]	109	58.9 (24-84)	INS	PD (45); dystonia (48); tremor (12); pain (3); epilepsy (1)	2-6	R	No	No
Pepper, 2013[33]	100	INS	Yes	INS	3-7	R	Yes	Yes
Schlaepfer, 2013[35]	7	INS (3-8)	INS	MDD (7)	2	P	No	No
Ackermans, 2011[26]	6	12.0 (12)	INS	TS (6)	≤7	P	No	No
Vergani, 2010[40]	141	55.2 (9-120)	Yes	PD (141)	2-3	R	No	No
Mehrkens, 2009[41]	12	60.0 (37-90)	Yes	Dystonia (12)	3-5	R	No	No
Owen, 2007[42]	32	3.0 (INS)	INS	Pain (32)	7	P	No	No
Hamani, 2006[43]	21	INS (108 max)	INS	Pain (21)	5	R	No	No
Constantoyannis, 2005[38]	26	24.0 (6-60)	Yes	INS	3-5	P	Yes	No
Green, 2005[44]	7	20.6 (12-36)	INS	Pain (7)	Few days	P	No	No
Bojanic, 2004[28]	86	INS	Yes	PD (42); dystonia (16); pain (16); tremor (6); MS (6)	7	R	Yes	No
Temel, 2004[11]	106	42.6 (INS)	Yes	PD (90); tremor (10); pain (3); TS (2); HD (1)	7	R	No	No
Oh, 2002[45]	79	33.0 (8-84)	Yes	PD (53); tremor (9); pain (9); epilepsy (3); dystonia (3); HD (1); MS (1)	7	R	No	No
Vesper, 2002[46]	38	12.0 (INS)	INS	PD (38)	4	R	No	No
Vercueil, 2001[36]	19	45.9 (6-132)	INS	Dystonia (19)	INS	R	No	No
Kumar, 1997[29]	68	78.0 (6-180)	INS	Pain (68)	5-7	P	No	No
Benabid, 1996[37]	117	INS (6-90)	Yes	PD (80); tremor (27); dystonia (6); MS (4)	7	R	No	No
Levy, 1987[30]	141	81.6 (24-168)	INS	Pain (141)	1 to several days	R	No	No
Dieckmann, 1982[31]	46	INS (6-54)	INS	Pain (46)	INS	P	No	No
Plotkin, 1982[32]	60	INS (6-42)	Yes	Pain (60)	At least 7 d	P	No	No

HD, Huntington disease; INS, information not supplied; MDD, major depressive disorder; MS, multiple sclerosis; No., number; P, prospective; PD, Parkinson disease; PWS, Prader-Willi syndrome; R, retrospective; TS, Tourette syndrome.

RESULTS

Study Selection

The literature search yielded a total of 515 articles after duplicates were removed. After the first phase of screening, 352 articles were excluded, leaving 163 articles that underwent full-text review. After the second phase of screening, an additional 78 articles were excluded, yielding a total of 16 articles from our search strategy. An additional 7 articles were included from a search of reference lists, resulting in a total of 23 articles that were included in our study.[11,22,26-46] The process of study selection is represented in a PRISMA flowchart in Figure 1.[23] A list of the articles that were excluded after full-text review, with reasons for exclusion, can be found in **Text**, **Supplemental Digital Content B**.

TABLE 3. Outcomes of Studies Relating to Electrode Externalization and Infection

Author, year	No. of patients with infection	Infection rate	Indication (no. of patients)	Average time to infection (months)	Microbiology of infection (no. of infections)	Site of infection (no. of infections)	Management (no. of infections)	Increased risk? (*P* value)
Franco, 2018[34]	2	50.0	PWS (2)	4	INS	C (1), IPG (1)	A (1), RH (1)	NA
Boccard, 2017[39]	5	20.8	Pain (5)	INS	INS	INS	RH (6)	NA
Rosa, 2017[22]	3	2.9	PD (3)	6	*Staphylococcus aureus* (2), *Nocardia farcinica* (1)	IPG (3)	A, RH (3)	No (.054)[a]
Lee, 2014[27]	0	0	NA	NA	NA	NA	NA	NA
Pepper, 2013[33]	4	4.0	PD (3) tremor (1)	2.1	Gram negative rod (1), *Klebsiella pneumoniae* (1), coagulase-negative *Staphylococcus*, *Enterobacter intermedius*, and *Candida famata* (1)	IPG (1), IPG and BH (1), BH (2)	RH (4)	No (.78)
Schlaepfer, 2013[35]	2	28.6	MDD (1)	INS	INS	IPG (2)	INS	INS
Ackermans, 2011[26]	1	16.7	TS (1)	INS	*S. aureus* (1)	IPG (1)	A (1)	NA
Vergani, 2010[40]	8	5.7	PD (8)	INS	*S. aureus* (2), *Pseudomonas* (2), *S. epidermidis* (2)	Intracranial lead (2), IPG (6)	RH (3); A (3); A, RH (2)	NA
Mehrkens, 2009[41]	1	8.3	Dystonia (1)	0.5	INS	BH (1)	RH (1)	NA
Owen, 2007[42]	2	6.3	Pain (2)	INS	INS	INS	A (2)	NA
Hamani, 2006[43]	1	4.8	Pain (1)	INS	INS	INS	RH (2)	NA
Constantoyannis, 2005[38]	4	15.3	INS	INS	INS	INS	A/RH (INS)	Yes (.003)
Green, 2005[44]	1	14.3	Pain (1)	INS	INS	INS	A, RH (1)	NA
Bojanic, 2004[28]	3	3.5	Pain (3)	INS	N/A	IPG (3)	INS	No (<.099)
Temel, 2004[11]	4	3.8	PD (4)	1.9	*S. aureus* (4)	IPG (2), IPG and C (1), C (1)	A (2); A, D, RH (2)	NA
Oh, 2002[45]	10	12.7	Dystonia (2); pain (2); PD (5); tremor (1)	10.2	*S. aureus* (2), *Mycobacterium fortuitum* (1), *Enterobacter* (1), *Pseudomonas* (1)	BH (3), BH and C (1), IPG (1), C (5)	A, D (1); A, D, RH (5); RH (4)	NA
Vesper, 2002[46]	2	5.3	PD (2)	INS	INS	IPG (2)	RH (2)	NA
Vercueil, 2001[36]	1	5.3	Dystonia (1)	INS	INS	BH (1)	RH (1)	NA
Kumar, 1997[29]	4	5.9	Pain (4)	INS	INS	INS	A (3); RH (1)	NA
Benabid, 1996[37]	3	2.6	INS	INS	INS	C (3)	RH (3)	NA
Levy, 1987[30]	17	12.1	Pain (17)	INS	*S. epidermidis* (9), *S. aureus* (6), *Propionibacterium acnes* (2), Group B *Streptococcus* (1), *Micrococcus* (1), *Enterobacter cloacae* (1)	BH (19), IPG (3), C (1)	A (4); A, D (8); A, RH (11)	NA
Dieckmann, 1982[31]	2	4.3	Pain (2)	INS	INS	INS	INS	NA
Plotkin, 1982[32]	2	3.3	Pain (2)	7.5	INS	C (1) Scalp, not specified (1)	A (1); A, RH (1)	NA

A, antibiotics; BH, on scalp overlying burr hole; C, on scalp overlying connecting cable; D, debridement; INS, information not supplied; IPG, internal pulse generator; MDD, major depressive disorder; NA, not applicable; No., number; PD, Parkinson's disease; PWS, Prader-Willi syndrome; RH, removal of hardware; TS, Tourette syndrome.

[a] Although this study did not include a control group, they performed a comparison of the incidence of infection in their cohort with rates of infection previously reported in the literature.

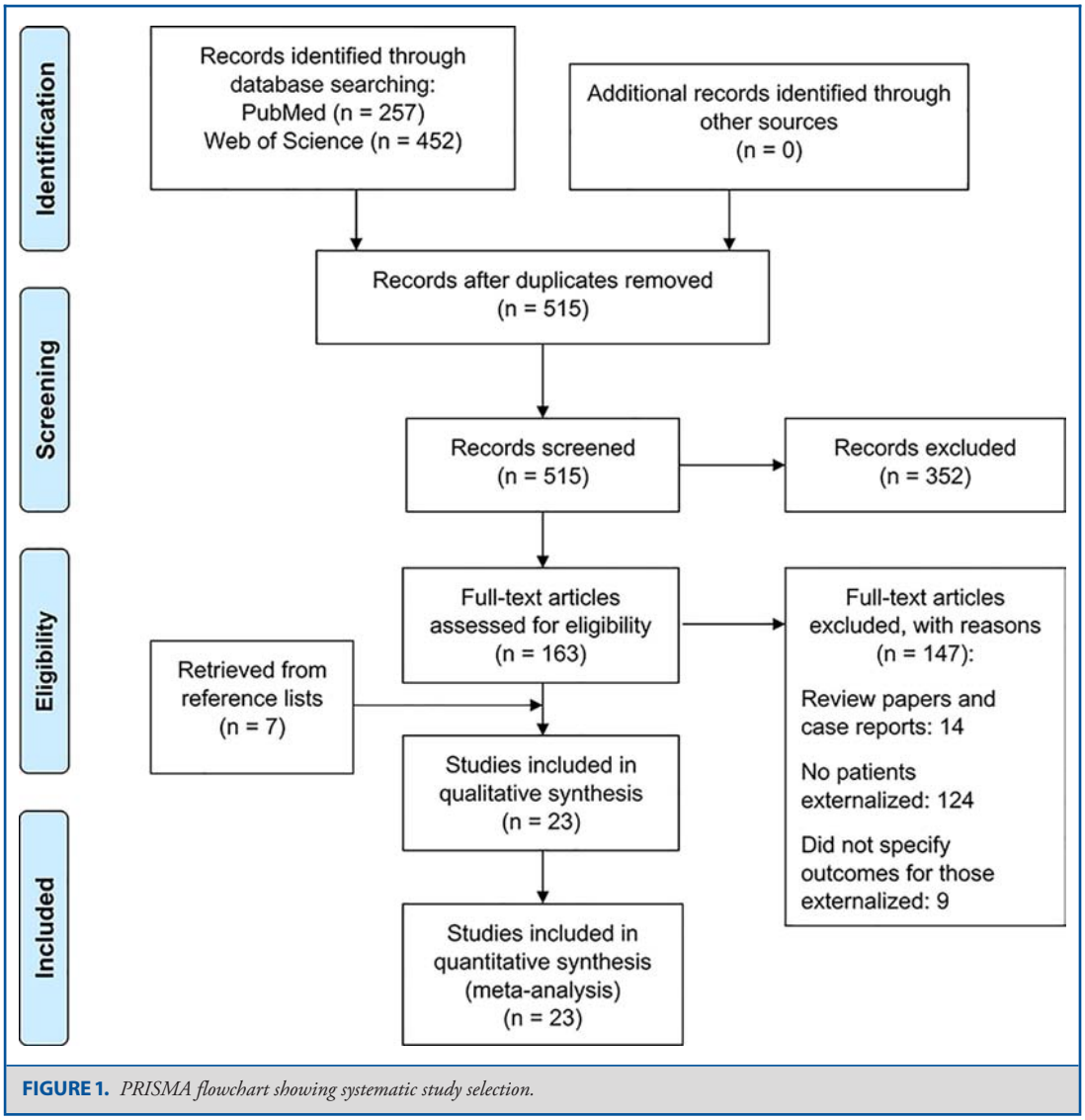

FIGURE 1. *PRISMA flowchart showing systematic study selection.*

Study Characteristics

The study characteristics of the selected articles are presented in Table 2, comprising 23 studies between 1982 and 2018, with a total of 1354 patients (mean: 58.9; range: 4-141) who underwent externalization of deep brain electrodes prior to full internalization. A total of 21 studies (91.3%) reported follow-up times (mean: 36.5 mo; range: 3-180 mo). In total, 10 out of the 23 studies mentioned the use of antibiotic prophylaxis before surgery as well as during the period of externalization. Among those studies that distinguished the diagnosis of their patients who underwent externalization, 594 (48.4%) underwent DBS for PD, 430 (35.0%) for pain, 104 (8.5%) for dystonia, 64 (5.2%) for tremor, 11 for multiple sclerosis (0.9%), 8 (0.7%) for Tourette syndrome, 7 (0.6%) for major depressive disorder, 4 (0.3%) for epilepsy, 4 (0.3%) for Prader-Willi syndrome, and 2 (0.2%) for Huntington disease. Duration of externalization mostly ranged from 1 to 7 d, with the exception of 1 study that included some patients who were externalized for more than 7 d.[32] A total of 14 studies were retrospective in design and 9 were prospective. Only 3 studies (15.4% of patients) included a control group of patients who were not externalized. Although many studies provided a detailed account of infectious disease history, only 2 studies (8.7%) referenced a specific definition or criteria by which infection was diagnosed.

Main Findings

The main findings of the included studies can be found in Table 3. A total of 82 patients (6.1%) were diagnosed with 91 infections following lead externalization, with rates of infection ranging between 0% and 50%. The rate of infection was 5.6%

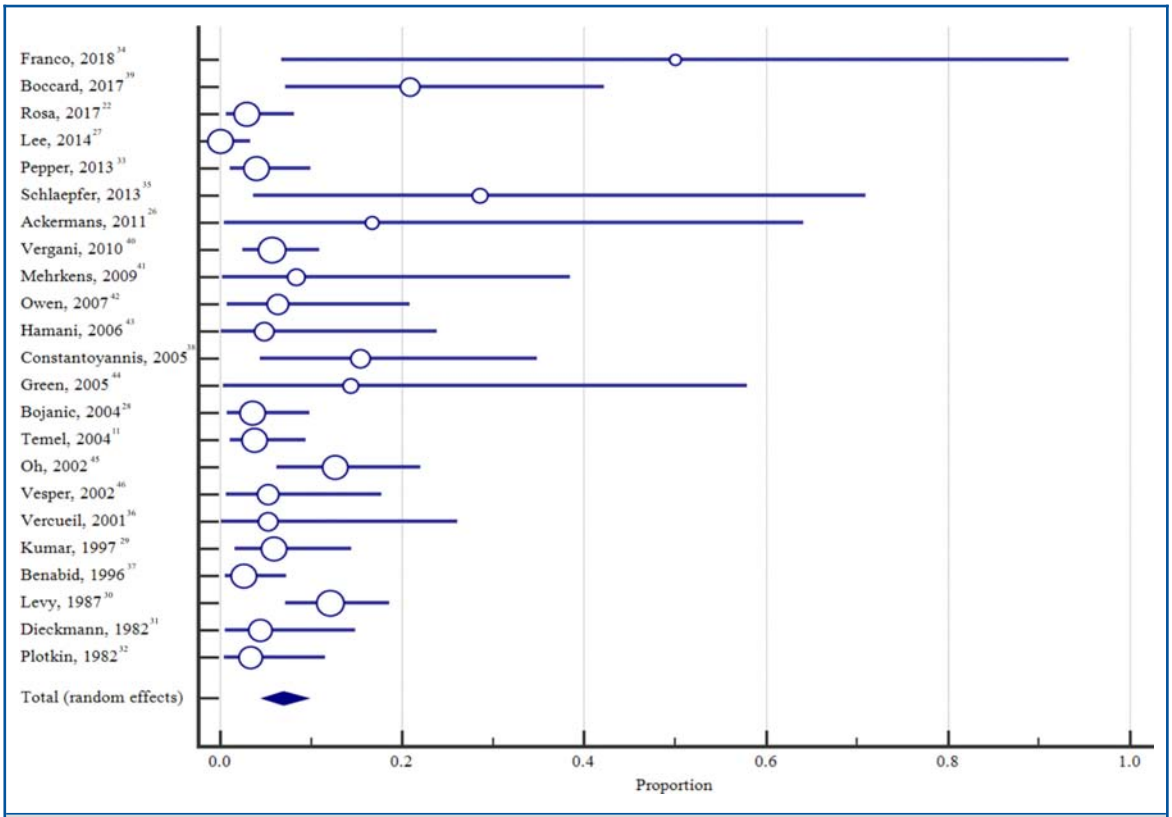

FIGURE 2. *Forest plot of pooled estimate of infection across all studies.*

in retrospective studies and 7.8% in prospective studies. Studies with an externalization period of strictly <7 d[27,34,35,38,40,41,43,46] had a rate of infection (20/358 [5.6%]) that was slightly less than the rate of infection in studies with an externalization period of ≥7 d (30/510 [5.9%]).[11,26,28,32,37,39,42,45] Average time to infection was 4.6 mo (range: 0.5-10.2); however, only 7 studies reported this information. The indication with the highest rate of infection after DBS surgery was Prader-Willi syndrome (2/4 [50.0%]), followed by major depressive disorder (1/7 [14.3%]), Tourette syndrome (1/8 [12.5%]), pain (39/430 [9.1%]), PD (25/594 [4.2%]), dystonia (4/104 [3.8%]), and tremor (2/64 [3.1%]). The overall rate of infection for patients with movement disorders (PD, tremor, and dystonia) was 4.1% (31/762 patients). Patients who underwent DBS for multiple sclerosis (11 patients), epilepsy (4 patients), or Huntington disease (2 patients) did not have any infections.

In those studies that localized the site of infection, 26 (38.8%) were on the scalp overlying the burr hole, 25 (37.3%) were at the IPG, 12 (17.9%) were on the scalp overlying the connecting cable, 2 were intracranial at the site of lead, and 3 infections involved more than 1 site. A total of 7 studies noted positive findings on bacterial culture. The most common pathogens identified included *Staphylococcus aureus* and *S. epidermidis*. In those studies that described management of infection, all but 2 studies (89.5%) reported removal of hardware as a form of management. In total, 3 studies[22,28,33] concluded that there was no increased risk of infection with externalization and 1 study concluded otherwise.[38]

Meta-Analysis

The pooled proportion of externalized patients that developed an infection was 6.9% (95% CI: 4.7%-9.5%) (Figure 2). Between-study heterogeneity was assessed using the I^2 measure of inconsistency and was found to be 62.2% (95% CI: 40.7-75.9; $P < .0001$), consistent with a moderate to high level of heterogeneity. Among those studies with a nonexternalized control group, the pooled relative risk estimate for infection in patients with an externalization period was 1.2 (95% CI: 0.2-8.0; $P = .825$) (Figure 3), with moderate to high level of heterogeneity across studies ($I^2 = 73.9\%$ [95% CI: 12.8-92.2]; $P = .022$). Unfortunately, this analysis was inadequately powered to detect if there was no difference in the incidence of infection between patients who underwent externalization and those that did not.

When determining whether study design (retrospective vs prospective) had an effect on the rate of infection, metaregression analysis found that difference between the 2 groups was statistically nonsignificant ($P = .681$). Similarly, metaregression analysis

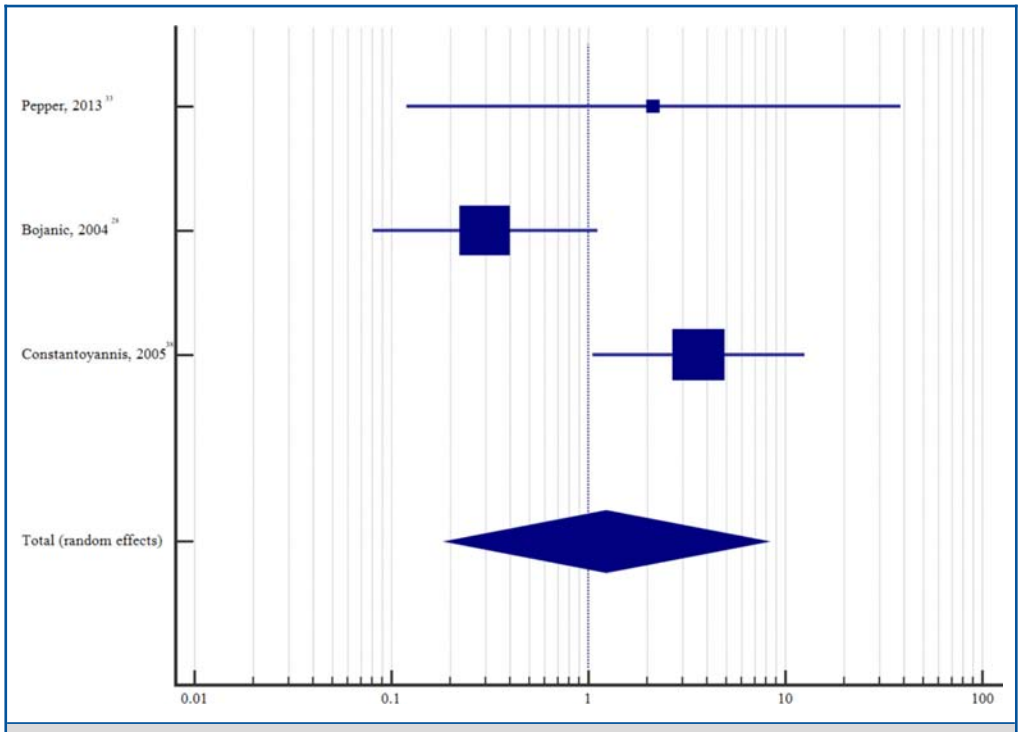

FIGURE 3. *Forest plot of the relative risk of infection among studies with a nonexternalized control group.*

found that the rate of infection was not significantly different ($P = .277$) between studies with a duration of externalization <7 d and those with a duration of externalization of ≥7 d.

DISCUSSION

Key Results and Comparison with the Literature

The externalization of deep brain electrodes provides the opportunity to test the efficacy of DBS for new indications and to acquire neurophysiological data. As with any medical intervention it is critical that patients have sufficient understanding of the risks of the intervention prior to consenting to treatment. Here, we found that the average rate of infection for individuals who undergo an externalization prior to full DBS system implantation is 6.9%.

There is substantial variation in the published incidence of infection following DBS, with rates ranging from approximately 1.5% to 22.2%.[4-21] Previous systematic reviews and/or meta-analyses on DBS-related infections have calculated rates of infection ranging between 4.7% and 6.1%[2,3,52]; however, comparing our results with that of published estimates is problematic because of differences in study design, population, and follow-up time in the included articles. In particular, a large proportion (35.0%) of the patients that underwent externalization were patients that were being treated for pain, which appears to be an indication that is more susceptible to infection (9.1% rate of infection) than that of other indications for DBS such as PD (4.2% risk of infection). In contrast, patients who underwent DBS for pain are generally not represented in the previously published meta-analyses, which mostly comprise studies with no period of externalization.[2,3,52] Given that there are known differences in infection rate based on the indication for DBS,[2,53] we can compare infection rates based on underlying disease. In their systematic review of hardware-related complications of DBS, Jitkritsadakul et al[2] identified 96 articles, comprising 8983 patients that met their selection criteria. They found that established indications for DBS, such as PD (5.8% rate of infection), had lower rates of hardware-related infection, than that of new indications for DBS, such as Tourette syndrome (11.7% rate of infection).[2] Consistent with these results, we found that patients that were externalized prior to permanent DBS implantation for movement disorders such as PD (4.2% rate of infection) and tremor (3.1% rate of infection) had lower rates of infection than patients treated for psychiatric diseases, such as Tourette syndrome (12.5%) and major depressive disorder (14.3%) (Table 4). Overall, when considering just those patients that underwent externalization prior to DBS implantation for movement disorders (PD, tremor, and dystonia), we found that the incidence of infection in these patients (4.1%) was less than the 4.7% average rate of infection reported by Bhatia and colleagues[3] in their meta-analysis of infections for movement disorders.

TABLE 4. Rates of Infection by Indication: Comparing Our Results With the Literature

DBS indication	Rate of infection with externalization, % (infection/total)	Rate of infection from the literature, % (infection/total)[a]
PD	4.2 (25/594)	5.8 (85/1454)
Pain	9.1 (39/430)	INS
Dystonia	3.8 (4/104)	7.4 (44/592)
Tremor	3.1 (2/64)	INS
MS	0 (0/11)	INS
TS	12.5 (1/8)	11.7 (16/137)
MDD	14.3 (1/7)	INS
Epilepsy	0 (0/4)	11.5 (16/139)
HD	0 (0/2)	INS
PWS	50 (2/4)	INS

DBS, deep brain stimulation; PD, Parkinson disease; INS, information not supplied; MS, multiple sclerosis; TS, Tourette syndrome; MDD, major depressive disorder; HD, Huntington disease; PWS, Prader-Willi syndrome.
[a]Literature rates of infection as reported by Jitkritsadakul et al[2] in their review of hardware-related complications of DBS.

Studies with a Control Group of Nonexternalized Patients

In order to further assess whether a period of externalization contributes to an increased risk of infection, we performed an additional meta-analysis on 3 studies that included a control group of patients that did not undergo a period of externalization (Table 5).[28,33,38] Although rates of infection between the 2 groups were similar (5.2% for those externalized vs 6.0% for those nonexternalized), the meta-analysis was inadequately powered and therefore at high risk of a Type II error.[54] A comparison with larger sample sizes will be needed to sufficiently determine if there is in fact no significant difference in infection between the 2 groups.

The most common location of infection for the nonexternalized patients was at the site of the IPG (specified in 7/7 patients), which is consistent with previously published studies.[2,52] Similarly, in their series of 420 patients who underwent DBS without any externalization period, Sillay and colleagues[6] reported that 14 out of 19 patients with infection (73.7%) had their infection located at the site of the IPG. In contrast, across all 23 of our included studies, almost equal numbers of infection were reported at the IPG (37.3%) and the scalp overlying the burr hole (38.8%) in patients who underwent an externalization period. This may suggest that although the process of electrode externalization may not confer an increased risk of infection compared to direct internalization, it does seem to influence the site of infection, possibly increasing the relative risk of cranial site infections.

Infection Rates for Commonly Externalized Devices in Neurosurgery

The externalization of therapeutic and monitoring devices is well-established in neurosurgical practice. Intracranial pressure (ICP) monitoring and external ventricular drains (EVDs) are fundamental to the care of patients in the neurocritical setting but are not without risk. Infection is the most common complication encountered with ICP monitors, with an average rate of infection of 10%.[55] Although fiberoptic ICP monitors are associated with a decreased rate of infection,[56] EVDs, considered the "gold standard" of ICP monitoring, have been found to be associated with an 8.8% average rate of infection.[57] The most recent study on this topic reported a 3.1% infection rate among 389 consecutive patients who underwent EVD placement.[58] In the subspecialty of functional neurosurgery, the technique of electrode externalization is already commonly used for monitoring seizure activity in patients with epilepsy, often for weeks at a time. The complications of this procedure are not negligible, with reported rates of infection ranging between 2% and 10%.[59]

Limitations

This is the first comprehensive systematic review and meta-analysis of electrode externalization and its associated rates of infection. Because few studies have explicitly investigated the risk of electrode externalization, the majority of our data was extracted

TABLE 5. Outcomes of Studies With an Externalized and Nonexternalized Group

Author, year	Infected/ externalized (%)	DBS indication of infected (%)	Site of infection (%)	Infected/ nonexternalized (%)	DBS indication of infected (%)	Site of infection (%)	Increased risk with externalization? (*P* value)
Pepper, 2013[34]	4/100 (4.0%)	3 PD (INS); 1 tremor (INS)	IPG (25%), IPG and BH (25%), BH (50%)	0/23 (0%)	NA	NA	No (.78)
Constantoyannis, 2005[39]	4/26 (15.3%)	INS	INS	5/118 (4.2%)	INS	INS	Yes (.003)
Bojanic, 2004[29]	3/86 (3.5%)	3 pain (18.8%)	IPG (100%)	7/60 (11.7%)	3 PD (13.0%); 4 dystonia (19.0%)	IPG (100%)	No (<.099)

BH, on scalp overlying burr hole; DBS, deep brain stimulation; INS, information not supplied; IPG, internal pulse generator; NA, not applicable; PD, Parkinson disease.

from retrospective case series with no control group, varying sample sizes, and follow-up times. Although we provide a comparative analysis from studies that included comparator groups, the comparison of infection rates should be interpreted with caution as the number of subjects is small and the effect size is likely small, limiting the power of this comparison and predisposing to Type II error. Larger sample sizes are needed in order to determine if there is in fact a significant difference in infection rate between the groups. Moreover, the profile of patients evaluated in our pooled analysis does not reflect the overall profile of patients who undergo DBS implantation, with a predominant indication for PD. In the pooled data, 35% of externalized patients had pain, 0.7% had Tourette syndrome, and 0.3% had Prader-Willi syndrome, which are not established DBS indications and are associated with skin picking,[60,61] which may in and of itself change the relative risk of infection. Additionally, studies varied in their use of antibiotic prophylaxis as well as their definition of infection. Despite these limitations, our study serves as an important starting point for understanding the risk of infection with externalization and its comparison to nonexternalized cohorts.

CONCLUSION

The results of our systematic review and meta-analysis found a 6.9% risk of infection with externalization of deep brain electrodes, which is comparable to the historical rate of infection for individuals without an externalization period. Although this is the best estimate currently available, further research is needed before this information can be confidently used in the clinical setting.

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Supplemental Digital Content. Text. Appendix A, Literature review search strategy. Appendix **B**, Articles excluded and reasons for exclusion after full-text review.

COMMENT

This metanalysis reflects the great work by its authors, who effectively analyzed the data from the literature about the infection rate after the externalization of DBS electrode. As noted by the authors, certain limitations may affect the conclusion, however the literature review and analysis results are very comprehensive and well conducted, and it is an excellent addition to the current literature. The infection rate remained variable from center to center. In general, the incidence of infection can be reduced by the applied surgical techniques, whether in DBS or spinal cord stimulation. The pacemaker location remains the leading site of DBS infection. Furthermore, pacemaker replacement is shown to carry a higher risk of infection than a primary DBS system implant, and this can be reduced by surgical technique modification.[1]

In the context of DBS electrode externalization various benefits, this current study well supports the safety of its utilization. Throughout history, the science of brain stimulation has benefited significantly from studying the biomarkers of deep brain neuronal structures after a period of the externalized electrode. Enabling scientists to probe different neural circuits has resulted in the advancement of the science in various neurological and functional disorders. The technology advancement is directed toward a wireless technology that could replace the need for deep brain electrode externalization. Many thanks to the authors for providing such a comprehensive, detailed review and analysis.

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