Retrospective Review

Infectious Complications Related to Intrathecal Drug Delivery System and Spinal Cord Stimulator System Implantations at a Comprehensive Cancer Pain Center

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Background: Intrathecal drug delivery (IDD) and spinal cord stimulator (SCS) systems are implantable devices for the management of both chronic and cancer pain. Although these therapies have favorable long-term outcomes, they are associated with occasional complications including infection. The incidence of infectious complications varies from 2 - 8% and frequently requires prolonged antibiotics and device revision or removal. Cancer patients are particularly susceptible to infectious complications because they are immunocompromised, malnourished, and receiving cytotoxic cancer-related therapies.

Objective: Determine if cancer pain patients have a higher incidence of infectious complications following implantation of IDD or SCS systems than non-cancer pain patients.

Study Design: Retrospective chart review.

Setting: Single tertiary comprehensive cancer hospital.

Methods: Following local Institutional Review Board (IRB) approval, we collected data on infectious complications for IDD and SCS systems implanted at MD Anderson Cancer Center for the treatment of cancer and chronic pain. The examined implants were performed from July 15, 2006, to July 14, 2009. In addition, we obtained data regarding patient comorbidities and perioperative risk factors to assess their impact on infectious complications.

Results: One hundred forty-two devices were implanted in 131 patients during the examined period. Eighty-three of the devices were IDD systems and 59 were SCS systems. Eighty percent of the patients had a diagnosis of cancer. Four infectious complications were noted with an overall infectious risk of 2.8%. The infection rate was 2.4% for IDD systems versus 3.4% for SCS systems ($P = 1$). All infections were at the implantable pulse generator (IPG) or pump pocket site. The rate of infection was 2.7% for cancer patients and 3.3% for non-cancer patients ($P = 1$). Neither the perioperative administration of prophylactic antibiotics ($P = 0.4$) nor the National Nosocomial Infection Surveillance (NNIS) risk level for individual patients ($P = 0.15$) were statistically associated with infectious complication. The mean surgical time was longer for cases with infection at 215 ± 93 minutes versus 132 ± 52 minutes for those without infection which was statistically significant ($P = 0.02$).

Limitations: The major limitation of this study is that it was a retrospective analysis. An additional limitation is that 51(38.9%) of our patients either died or were lost to follow-up during the year following implantation which may have led to an underestimation of our infection rates.

Conclusions: The experience of this tertiary cancer pain center demonstrates that infectious complications following implantation of IDD and SCS systems are relatively rare events in cancer patients. Contrary to our initial hypothesis, no difference was found in the infection rate between cancer and non-cancer patients. The main factor associated with increased risk of infectious complications was increased surgical time, indicating a need to minimize patient time in the operating room. The low infectious complication rate seen in this series compared to previous reports in non-cancer patients is likely multifactorial in nature.

Key Words: Spinal cord stimulation, intrathecal drug delivery, implantable pain therapies, neuromodulation, pain procedures, pain, complications, infection, surgical site infection

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Moderate to severe pain is a frequent occurrence in cancer patients both from the tumor itself and from cancer-related treatments. Generally, this pain is initially managed using the World Health Organization (WHO) "pain ladder," moving from non-opioid pain relievers to strong opioid medications as the pain increases (1). Unfortunately, approximately 14% of patients are not able to achieve effective pain relief using this paradigm (2,3). In these cases, implantation of intrathecal drug delivery (IDD) and spinal cord stimulator (SCS) systems can be an effective strategy for the management of pain. Previous work has demonstrated that these devices have specific efficacy in the treatment of cancer related pain (4-10). Although serious complications following implantation of these devices are relatively rare, a potentially devastating complication in cancer patients is infection due to their immunocompromised state. The most common post-operative infection for these devices is a surgical site infection (SSI). In the context of implantable devices, SSIs are defined as infections that occur within one year after implantation if the device is not manipulated and if the infection appears to be related to the operation (11). The Centers for Disease Control (CDC) classification system for SSIs includes 3 specific subtypes of infections: superficial-incisional, deep-incisional, and organ space. Superficial-incisional SSIs often do not require re-hospitalization and are instead frequently diagnosed in the outpatient setting during post-discharge surveillance. Collectively, deep incisional and organ space infections are known as "invasive" SSIs and are serious infections that typically require hospitalization, intravenous antibiotic therapy, and possibly device explantation (12).

General risk factors for SSIs that are pertinent to cancer patients include leukopenia associated with the cancer or cancer therapy, diabetes mellitus, debilitated status, poor nutritional status, smoking, and possibly corticosteroid use (12-14). In addition, cancer patients frequently undergo treatment with chemotherapeutic agents and radiation, both of which can delay wound healing, increasing the risk of infection. The risk of SSIs is also related to perioperative factors such as National Nosocomial Infection Surveillance (NNIS, now the National Health Safety Network or [NHSN]) risk index, administration of appropriate and timely pre-operative antibiotics, and length of surgical procedure. To this end, the CDC and groups specializing in neuromodulation have published practice guidelines for infection risk mitigation when implanting IDD and SCS systems (12,15,16).

The reported rate of infection following IDD and SCS system implantation varies from 2% to 8% (4,12,16-23). This appears consistent with SSI rates from other implanted devices such as cerebral spinal fluid shunts and pacemakers (12). Almost all previous infectious complications data related to IDD and SCS systems were obtained from non-cancer patients. From the primary literature and meta-analyses cited above, only the Smith et al (4) work specifically cited the infectious complication rate for cancer patients. This study only included cancer patients and reported one infection following 56 IDD system implantations. Several other studies reported the inclusion of a small number of cancer patients for both IDD and SCS system therapies, but the infection rates in this subpopulation were not specifically listed. As such, little is currently known regarding the risks of infectious complications following device implantation in cancer patients.

The purpose of this study was to determine whether the risk of infectious complications following IDD or SCS system implantation is different with cancer and non-cancer patients. We hypothesized that cancer patients would have increased rates of infectious complications and that these infections would be directly associated with untimely administration of pre-operative antibiotics, NNIS risk level, and duration of surgery.

Methods

This study was approved by the University of Texas MD Anderson Cancer Center Institutional Review Board (IRB) in Houston, Texas. Waivers of informed consent and authorization were not obtained because this was a retrospective study that involved no diagnostic or therapeutic interventions, as well as no direct patient contact. A thorough retrospective chart review was carried out for each patient implanted with an IDD or SCS system at MD Anderson Cancer Center from July 15, 2006, to July 14, 2009. Implanted patients were initially identified using the electronic surgery scheduling list and departmental billing data. HIPAA compliance was maintained by replacing the name and medical record number with unique study numbers in the analytical file. Subsequent patient demographic and medical information was abstracted from the MD Anderson electronic health record system. Preoperative data obtained includes gender, age, cancer diagnosis, status of cancer treatment, and indication for the device. Perioperative data obtained includes device implanted, surgical skin preparation, preoperative antibiotic prophylaxis, duration of surgery, NNIS risk level, and wound class. Post-operative data obtained

includes presence of infection, time from surgery to infection, site infected, CDC SSI classification, treatment of infection, action taken with the device, and treatment outcome. For the purpose of this study, post-operative infection surveillance was set at the standard one year following implantation of a device (11). For data analysis, the mean or median was reported for the continuous variables and proportions were estimated for categorical variables. The Wilcoxon rank-sum test was used to assess association for continuous variables. The categorical variables were analyzed using the Fisher's exact test. SAS version 9.2 (SAS Institute Inc.; Cary, NC) was used to carry out all analyses.

Results

Demographic Data

A total of 142 IDD or SCS system implants were performed on 131 patients at MD Anderson Cancer Center during the reported time period. The total number of implants is greater than the total number of patients because 8 patients had 2 or more surgical procedures. During the year following implantation, 33 patients died and 18 patients were lost to follow-up. The median age at implantation was 53 years. The female to male distribution was 53% to 47%, respectively. Of the 142 implanted devices, 58% were IDD systems and 42% were SCS systems. A cancer diagnosis was present for 80% of the patients in the study.

Infection and Perioperative Data

A total of 5 infections occurred during the reported time period. However, one IDD system infection was excluded because it occurred 11 weeks after the implantation and after the IDD system surgical site had been violated for a medication refill. No signs of infection were noted prior to the medication change. Therefore, the infection could not be directly tied to the implantation because the surgical site had been violated and the medication change was temporally linked to the infection. Of note, the details of the IDD system refill are unknown since it took place at another facility near the patient's home. To the best of our knowledge, the IDD system was refilled with a monotherapy admixture of ziconotide. This admixture of ziconotide is a potential cause of the infection; however, it appears more likely to be related to the refill technique given the fact that the IDD system pocket was obviously infected at the time of explantation.

All remaining infections were surgical site infections (SSI; Table 1). The infections all occurred at the

Table 1. *Patients with IDDS or SCS Implantation Related Infections*

Pt.	Age	Sex	Device	Diagnosis	Active Cancer	Skin Prep	TAA*	Antibiotic Administered	NNIS Risk Level	Time to Infection	Infection Site	CDC SSI Classification	Wound Culture	Treatment	Outcome
1	56	M	SCS	Non-Cancer: Angina	N/A	DuraPrep	Yes	Cefazolin	1	13 d	IPG pocket	Superficial Incisional	None obtained	PO and topical antibiotics	Infection Resolved
2	39	M	SCS	Lymphoma; CIPN	Yes	DuraPrep	Yes	Cefazolin	2	29 d	IPG pocket	Superficial Incisional	MRSA	Explanted	Reimplanted
3	79	M	IDDS	Metastatic sacral chordoma	Yes	Chlorhexidine + Alcohol	No	None documented	1	18 d	Pump pocket	Superficial Incisional	P. aeruginosa	Explanted	Not Reimplanted
4	53	F	IDDS	Sacral chordoma	Yes	DuraPrep	Yes	Cefazolin	1	1 d	Pump pocket	Superficial Incisional	No Growth	IV antibiotics	Infection Resolved

Note: All four patients had Clean Wound Class. *Timely Antiobiotic Administered; M: male; F: female; SCS: Spinal cord stimulator; IDDS: Intrathecal drug delivery system; CIPN: Chemotherapeutic induced peripheral neuropathy; IPG: Implanted pulse generator; NNIS: National nosocomial infections survey; SSI: Surgical site infection; MRSA: Methicillin resistant Staphylococcus aureus

implanted pulse generator (IPG) or IDD system pump insertion site. The infections occurred from one to 29 days post-operation. The overall infection rate was found to be 2.8% (Table 2). The risk of infection for IDD and SCS systems was 2.4% and 3.4%, respectively. This was not statistically different (P = 1). Interestingly, the risk of infection was 2.7% among patients with cancer versus 3.3% for non-cancer patients. This was not statically significant (P = 1). The NNIS risk level was determined for each implantation: Risk level 0 was present for 22 cases (15%), level 1 for 115 cases (81%), level 2 for 5 cases (4%), and level 3 for zero cases. The NNIS risk level was not associated with risk of infection (P = 0.15). Inappropriate or untimely preoperative antibiotic prophylaxis was present for 17 (12%) of the cases, but was not associated with infection (P = 0.4). The mean duration of surgery was 215 ± 93 min for cases with infections versus 132 ± 52 for cases without infection. This difference was statistically significant (P = 0.02).

Discussion

Significant strides were made in the management of cancer-related pain with the release of the "pain ladder" by the WHO in 1986, with an update in 1996 (1). Using this ladder, most cancer patients quickly advance to the use of strong opioids. As such, opioids continue to be the mainstay treatment for cancer pain. Unfortunately, when the WHO pain ladder is utilized, effective pain control is not quickly achieved in approximately one third of patients (24). In addition, approximately 14% of patients do not achieve effective pain relief at any time (2,3). For this reason, many pain practitioners have incorporated a fourth step of interventional procedures (25). Our practice at MD Anderson Cancer Center has been to utilize interventional procedures not as a fourth step per se, but rather as techniques that can be utilized as appropriate at any time during patient care, which is consistent with previous publications (26).

Two procedural interventions that we commonly utilize in the treatment of cancer pain are IDD and SCS systems. IDD systems have been systematically studied for the treatment of cancer pain. In 2002, Smith et al (4) conducted a randomized trial comparing comprehensive medical management (CMM) to CMM plus an IDD system. A subsequent paper with extended follow-up of the same patients was published in 2005 (10). These studies found that CMM plus an IDD system produced statistically significant reductions in reported pain scores and opioid related toxicities. In addition, there was a trend towards increased survival in the group treated with CMM plus an IDD system, although the mechanism for this is still not clear. In contrast to IDD systems, no specific trials have evaluated the efficacy of SCS systems for the treatment of cancer pain. However, case reports have documented the efficacy of SCS in the treatment of chemotherapeutic induced peripheral neuropathy (9) and phantom limb pain (8). Although not specifically structured towards cancer patients, a 2005 randomized trial by North et al (23) demonstrated that that SCS is superior to repeated back operation in the treatment of failed back surgery syndrome. Following resection of spinal tumors, failed back surgery syndrome is relatively common, and in our practice is well treated with SCS.

Infection following the implantation of IDD and SCS systems is one of the most feared complications

Table 2. *Infection Related Covariate Analysis*

	Category	No Infection	Infection	P value
Cancer Status	No	29 (97.7%)	1 (3.3%)	1.00
	Yes	109 (97.3%)	3 (2.7%)	
IDDS vs. SCS	IDDS	81 (97.6%)	2 (2.4%)	1.00
	SCS	57 (96.6%)	2 (3.4%)	
Timely Antibiotic Administration	No	16 (94.1%)	1 (5.9%)	0.40
	Yes	122 (97.6%)	3 (2.4%)	
NNIS Risk Level	0	22 (100%)	0 (0%)	0.15
	1	112 (97.4%)	3 (2.6%)	
	2	4 (80%)	1 (20%)	
	3	0 (0%)	0 (0%)	
Duration of Surgery (minutes)		132 ± 52	215 ± 93	0.02

due to the high morbidity and potential mortality. The range of infectious complications in previous reports with IDD and SCS systems is from 2% to 8% (12,16-22). This number is relatively consistent with the 1% to 7% infection rate following implantable cardiac device placement (12). The overall risk of infection in this study for IDD and SCS system implantation was found to be 2.8%. This number is consistent with the 1.7% - 4.5% infection rate reported from other tertiary care centers with a high volume of IDD and SCS implantations (17,19). Of the 131 patients included in this study, 80 had follow-up for greater than one year, 33 died during the year, and 18 had follow-up for less than one year. All 4 infections occurred in the group that was followed for greater than one year. The average time at which patients were lost to follow-up was 3.4 months after implantation. Most of the patients who were not followed for a full year were transitioned to care near their homes and were subsequently lost to follow-up. We have no records of outside providers reporting an infection in any implanted patients. In a worst case scenario, if all lost to follow-up patients had infections plus the 4 known infections, then the total number of infections would be 22. This would represent a 16.8% infection rate. However, this rate is extremely unlikely since all patients were stable when lost to follow-up.

In other clean surgical procedures such as breast surgery, the risk of SSIs is elevated in cancer patients (3% - 15%) compared to non-cancer patients (3%) (27). The cause of this increased rate of SSIs in breast cancer cases compared to standard non-cancer breast surgery is incompletely understood. Using similar rationale, we expected an increased rate of infectious complications following implantation of IDD or SCS systems. Our patients commonly have multiple risk factors for SSI such as neutropenia associated with cancer or cancer therapy, diabetes mellitus, poor nutritional status, smoking, corticosteroid use, chemotherapy, and radiation therapy. The analysis of the data in this study rejected our initial hypothesis, demonstrating that the presence of a cancer diagnosis was not associated with an increased risk of infectious complications. The low infectious complication rate seen in cancer patients in this study is likely multifactorial in nature. Possible factors include both the high volume of implants performed at the institution and aggressive institutional perioperative infection control strategies.

We expected a lack of or untimely administration of pre-operative prophylactic antibiotics and increasing NNIS risk level to both be associated with increased risk of infection. However, neither of these covariates reached statistical significance which may speak to both the consistency of prophylactic antibiotic administration and the relatively low NNIS risk levels of the patients given their disease status. Of note, most of the patients in this study received 5 - 7 days of post-operative prophylaxis antibiotics in addition to their preoperative antibiotic.

The one factor that was significantly associated with infectious complications was the duration of surgery. Surgeries with infectious complications had a mean duration that was 83 minutes longer than cases without infection. This is consistent with a previous publication evaluating SSIs following spine surgery which found that increasing duration of surgery was an independent variable predicting SSI (28). Two of the 4 cases with SSIs reported reasons for the increased duration of surgery in their operative reports. Both of these cases were SCS implantations. For patient #1 in Table 1, prolonged programming was required to produce paresthesias in the correct anatomical distribution. For patient #2, both cervical and thoracic leads were placed and multiple lead movements were noted after anchoring which required extensive lead repositioning. For cases #3 and #4 in Table 1 which were both IDD system implantations, no causes for the increased duration of surgery could be identified in the operative or subsequent clinic notes. Collectively, these data do not answer the question of whether the extended duration of surgery is directly responsible for the increased risk of infection or whether the increased complexity of the surgical procedure associated with increased surgical time is driving the increased risk of infection. Regardless, limiting surgical time to the minimum required appears to be an appropriate risk reduction strategy at this time.

Previous work in the field of spine surgery has also demonstrated that repeat operations have a higher rate of SSIs (29). Our study included 8 patients who underwent 2 or more surgical procedures. These included implantation of both IDD and SCS systems, revisions of the original implantation, staged implantation of multiple SCS systems, and explantation with subsequent reimplantation of a SCS. Of the 8 patients with multiple procedures, no patients had SSIs on their second or subsequent operations. Given the limited number of repeat surgeries, it is difficult to determine whether prior surgeries increase the risk for SSIs in this patient population.

The single most important limitation of this study

is that it was a retrospective analysis. As with most retrospective analyses, the quality of the data is limited by completeness of the medical record for each patient. The most frequent medical record omission in this study was related to post-operative surveillance. Eighteen of the 131 patients had documented post-operative surveillance for less than one year after implantation which may have led to an underestimation of our infection rates. This significant loss to follow-up rate is due to the fact that our institution is a large tertiary comprehensive cancer center, and as such many of our patients come from distant locations for their cancer treatment and, in our case, device implantation. The patients will then generally return to their home following cancer treatment and device management will appropriately be transferred to a local provider.

In conclusion, effective management of cancer-related pain frequently requires a multimodal approach using a combination of opioid and adjuvant medications, complementary therapies, and interventional procedures. Both IDD and SCS systems can be used to effectively treat cancer-related pain. We initially hypothesized that cancer patients would have a higher risk of infection following implantation of IDD and SCS systems given their significant comorbidities. However, our hypothesis was proven incorrect, because cancer patients had infectious complication rates similar to patients with chronic non-cancer pain. The single variable associated with infectious complications in this study was increased duration of surgical time, suggesting a need to limit surgical time to the minimum required for safe implantation of either IDD or SCS devices.

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