Published in final edited form as:

Neuromodulation. 2018 October ; 21(7): 660–663. doi:10.1111/ner.12759.

Retrospective Analysis of Intrathecal Drug Delivery: Outcomes, Efficacy, and Risk for Cancer-Related Pain at a High Volume Academic Medical Center

Dawood Sayed, MD*, Forrest Monroe, MD*, Walter N. Orr, MPH*, Milind Phadnis, PhD, MS†, Talal W. Khan, MD, MBA*, Edward Braun, MD*, Smith Manion, MD*, and Andrea Nicol, MD*

*Department of Anesthesiology and Pain Medicine, University of Kansas, Medical Center, Kansas City, KS, USA; and †Department of Biostatistics, University of Kansas Medical Center, Kansas City, KS, USA,

Abstract

Objectives: Cancer pain is common and difficult to treat, as conservative medical management fails in approximately 20% of patients for reasons such as intolerable side-effects or failure to control pain. Intrathecal drug delivery systems (IDDS), while underutilized, can be effective tools to treat intractable cancer pain. This study aims to determine the degree of pain relief, efficacy, and safety of patients who underwent IDDS implantation at a multidisciplinary pain clinic.

Materials and Methods: A retrospective review was conducted of patients with an intrathecal pain pump implanted for malignant pain. Charts were reviewed for demographics, cancer type, pain scores before and after implantation, and intrathecal drugs utilized. A Wilcoxon Signed-Rank test was conducted on the paired differences of pain scores before and after implant. A regression analysis was conducted using a linear model to assess effects of demographic variables on change in pain scores.

Results: 160 patients were included in analysis. The median pain score was 7.1 at time of implantation and 5.0 at one-month postimplantation. For patients with both baseline and one-month pain scores available, the median decrease in pain was 2.5 ($p < 0.0001$). Pain scores three-month postimplantation did not significantly differ from one-month postimplantation. Median longevity was 65 days. Five patients had pumps explanted due to infection with a median time to pump extraction of 28 days.

Address correspondence to: Dawood Sayed, MD, Department of Anesthesiology and Pain Medicine, University of Kansas Medical Center, 3901 Rainbow Boulevard, Mail Stop 1034, Kansas City, KS 66160, USA. dsayed@kumc.edu.

Authorship Statements

Dr. Sayed served as the primary investigator, assisted with the manuscript preparation, data collection, and editing. Dr. Monroe served as a co-investigator and assisted with the manuscript preparation and data collection. Mr. Orr helped to prepare the manuscript and perform the literature search. Dr. Phadnis performed the statistical analysis. Drs. Khan, Braun, and Manion served as coinvestigators. Dr. Nicol served as a co-investigator and assisted with manuscript editing. All authors approved the final version of the manuscript.

Conflict of Interest: Dr. Sayed serves as a medical consultant for Flowonix. The remaining authors have no conflicts of interest to report.

For more information on author guidelines, an explanation of our peer review process, and conflict of interest informed consent policies, please go to www.wiley.com/WileyCDA/Section/id-301854.html

Conclusions: IDDS has the potential to improve cancer pain in a variety of patients and should be strongly considered as an option for those with cancer pain intractable to conservative medical management.

Keywords

Cancer pain; IDDS; intrathecal drug delivery systems; intrathecal pump; pain management; retrospective study

BACKGROUND

Epidemiologic data show that more than 1.6 million new cases of cancer are diagnosed in the United States per year, with more than half a million cancer deaths per year (1). With increasing incidence of cancer, it is imperative to focus attention not only on safe and effective treatments but also innovations or treatments to improve quality of life throughout the course of the disease, particularly when it comes to cancer-related pain. Most cancer patients experience pain at some point during the course of their disease and approximately 25% die in pain (2). The prevalence of cancer pain has been reported to be approximately 60–85%, and is the most commonly reported symptom in cancer patients (3–5). One survey of more than 5000 adult cancer patients across multiple countries reported a pain prevalence of 84%, with 94% of those experiencing pain classifying it as moderate to severe and 43% classifying their pain as severe (5). Pain also is experienced regardless of disease state, as high rates of pain were reported by patients with advanced, metastatic, or terminal diagnoses and by those who were receiving anticancer treatments (6). Cancer pain can significantly decrease patients' quality of life and has been associated with depression, poor general health, poor physical and social functioning, and impaired ability to perform activities of daily living (5,7,8).

The World Health Organization cancer pain ladder specifies that the treatment of cancer pain should begin with pharmacological management via the administration of nonopioids before moving to mild and strong opioids, as needed (9,10). However, approximately 5–15% of patients with metastatic cancer have pain refractory to pharmacologic management and require more advanced or invasive techniques of pain management (11–13). Thus, many patients do not achieve adequate pain control despite long-term or high opioid usage (14), which is concerning given current levels of opioid misuse in the United States (15,16). Earlier application of interventional pain management techniques for cancer patients can be recommended before considering high-strength opioids and may be beneficial (17). Specifically, implantable intrathecal drug delivery systems (IDDS) may be a viable option for those with refractory cancer pain to reduce opioid dosages while maintaining or improving pain management and reducing adverse side-effects.

IDDS has been shown to effectively reduce pain scores with better pain control and fewer adverse side-effects after both 4- and 12-week postimplantation, and has been associated with increased survival after six months (3,18). Another study found that pain scores decreased from 10 to 3.5 with administration of intrathecal analgesia, with patients showing functional improvements at 14 days with significant improvements in pain control and

quality of life (19). IDDS has also been associated with reduced opioid toxicity, with one study demonstrating a 50% decrease in toxicity for IDDS patients compared to a 17% reduction in those with conventional pain management such as opioids (3). Furthermore, IDDS has been associated with improvements in quality of life in those with cancer pain in the form of reduced drug-related side-effects. Specifically, those receiving IDDS reported lower instances of both fatigue and depressed levels of consciousness at four months when compared to conservative medical management (20). Intrathecal analgesia has also been associated with enhanced mental and physical function and improved mood (9). With improved six-month survival, decreased toxicity, better pain control, and fewer side-effects compared to conventional pain management, IDDS should be considered as an interventional pain management technique especially for those with cancer pain refractory to other pain management techniques.

Cancer pain can be difficult to treat and may often be intractable to conventional medical management. IDDS can be a versatile tool for the management of cancer pain across a variety of patients and types of cancers. This large retrospective study, spanning more than five years, aims to determine if patients who underwent implantation of IDDS at a multidisciplinary pain clinic in a large academic medical center had improved survival due to improved pain relief with IDDS. To our knowledge, this review is one the largest of its kind in regards to IDDS for cancer pain.

METHODS

A retrospective review was conducted following Institutional Review Board approval. The review included those who had an intrathecal pain pump implanted for malignant pain at our large academic multidisciplinary pain clinic between April 2008 and June 2016. Patients with an intrathecal pump implanted for nonmalignant pain were excluded.

Patients were identified by both manufacturer records of device implantation and a chart query for the CPT code for intrathecal pump implantation in order to cross reference our data to ensure accuracy. These lists were then combined and duplicates were excluded. Individual patient charts were reviewed from the time of decision to implant to the end of the record or patient death for data points including basic demographics, type of cancer, pain scores before and after implantation, and the intrathecal drugs utilized. Postimplantation data were categorized as 1-, 3-, 6-, and 12- month postimplant, utilizing the closest available visits to those time points.

Data were primarily collected from new patient clinic forms, pain and oncology clinic notes for outpatients, and physician and nursing notes for inpatients. Data were collected using a RedCap database and stored in Microsoft Excel.

Descriptive statistics related to patient demographics were calculated using the median and interquartile ranges (IQRs) for continuous variables and frequency counts for categorical variables. Pain scores before and after an IDDS implant were reported using the median scores and their corresponding IQR. All pain scores represent a patient's average pain at the time it was recorded. To assess effectiveness of IDDS, a Wilcoxon Signed-Rank test was

conducted on the paired differences of pain scores before and after implant. An additional Wilcoxon Signed-Rank test was performed to assess if patients who received bupivacaine had a greater reduction in pain score than patients not receiving bupivacaine. To assess the potential effect of demographic variables on change in pain scores, a regression analysis was conducted using a linear model. We further explored stability of pain scores over time by including pain scores on 43 patients taken at three-month postimplantation using a linear mixed model with a random intercept for each patient. All analyses were conducted in SAS (SAS Institute, Cary, NC, USA) with a significance level of 0.05.

RESULTS

One hundred sixty patients were included in the analysis. Of these patients, the median patient age was 58 years with a range of 18–79. Patients were 52% male and 48% female. Eighty-eight percent of patients were white, 6% black, 1% Hispanic, and 4% other or unknown. Almost all patients (93%) had documented metastatic disease, and over half had a primary cancer of the abdomen or pelvis with the most common type being pancreatic (20%). Pain score, with 0 representing no pain and 10 representing the worst pain imaginable, was collected at time of implant ($n = 152$) and one-month ($n = 83$), three-month ($n = 43$), six-month ($n = 19$), and one-year postimplant ($n = 7$) for those that had a recorded pain score. No reported pain score may indicate that either a pain score was not recorded during a particular patient visit or that the patient was lost to follow-up due to death or seeking care at another institution. The median pain score at the time of implantation was 7.1 ($n = 152$, IQR 6–8). For patients with one-month postimplantation follow-up data, the median pain score was 5 ($n = 83$, IQR 2–6). For patients whom both baseline and one-month pain score were available ($n = 80$), the median decrease in pain score was 2.5 (Wilcoxon $p < 0.0001$). Both age ($p = 0.666$) and gender ($p = 0.117$) were not associated with the reduction in pain scores. Additionally, of those who had both baseline and one-month pain scores, the median value for the reduction in pain score between those receiving bupivacaine (3, IQR 1–4; $n = 57$) and those that did not (2, IQR 0–4; $n = 23$) was not significantly different ($p = 0.56$). A linear mixed model analyses revealed that pain scores three-month postimplantation did not significantly differ from pain scores one-month postimplantation ($p = 0.384$). Figure 1 displays the mean pain score overtime.

A subgroup analysis was then performed to examine whether the effect on pain score was larger in patients implanted for severe pain compared to those who were implanted for intolerable side-effects of oral opioids but had mild to moderate pain. Excluding patients with a starting pain score less than 6, the median decrease in pain scores was 3.2 ($n = 56$, $p < 0.0001$). For patients with a recorded date of death ($n = 92$), the mean longevity with the intrathecal pump was 138 days and the median longevity was 65 days. Sixty-six percent of patients received bupivacaine in their intrathecal pump solution in addition to opioids. Eighty-seven percent of patients were documented to have received a patient-controlled bolus device. Five patients (3.1%) had their pumps explanted due to infection and, among these patients, the median time to pump extraction was 28 days (IQR 23–52 days).

DISCUSSION

Despite a significant body of literature supporting the utilization of IDDS in cancer pain, worldwide utilization of this treatment modality remains relatively low when compared to the number of patients who would potentially benefit (3,18,19). In a randomized prospective study, IDDS showed improved pain scores, decreased toxicity, and increased survival when compared to conventional medical management (3). Our study further demonstrates a significant reduction in pain scores after implantation. While this study did not explore efficacy across cancer types, the included patients had a wide array of cancer types such as pancreatic, colon, breast, prostate, and several other types of malignancies. Future research could explore if IDDS therapies work better for certain types of cancer diagnoses. In addition, we found that patients with an average pain score of greater than six experienced a greater reduction in pain score. Although reduction of opioid side-effects is one indication for IDDS implantation, this therapy seems to also be effective for those who do not achieve adequate pain control from oral opioids. Additionally, our study showed a median longevity of only 65 days after implantation. However, these data are likely skewed as this only includes patients with a recorded date of death ($n = 92$). This number does not include patients who are still living and those that did not have a recorded date of death who were lost to follow-up.

Recent guidelines in the National Comprehensive Cancer Network on Adult Cancer Pain also advise for the utilization of intrathecal infusion when patients either fail to achieve adequate analgesia or have intolerable adverse effects from conventional medical management (21). A number of reasons could possibly explain the underutilization of IDDS. The belief that systemic opioids provide adequate relief in the majority of patients with advanced cancer is likely not as true as once believed. Previous literature cites ineffective pain relief in up to 14% of patients suffering from cancer-related pain (11) and IDDS appears to be the most effective option in this patient population. Another reason for avoiding IDDS that is commonly cited by implanting physicians and oncologists alike is that IDDS is not a viable option in advanced cancer because of a higher than acceptable risk of infection in this immunocompromised population. However, an infection rate of 2.7% for IDDS in cancer patients was reported in a similar retrospective review, which was actually lower than the 3.3% rate of infection in noncancer patients at the same institution (22). Our review, with a 3.1% rate of infection, also supports a low infection rate for IDDS implantations in patients with cancer pain.

This study is limited by its retrospective design as data were obtained largely from physician notes, which in many cases did not include all the parameters of interest. There were also no standardized collection methods for chart data such as pain scores, as the scores recorded in the patient charts could have represented the patient's current pain, average pain, or maximum pain. Follow-up data were limited by the large referral area of our institution such that many patients received further care closer to home. With the well-demonstrated benefit of IDDS for cancer pain, we feel the equipoise is lacking to justify further randomized trials of IDDS vs. conventional medical management. Future prospective studies looking at outcome measures related to increased survival and quality of life in patients who are referred to a pain specialist at earlier points in the disease process are needed to further

strengthen the case for multidisciplinary pain management in general and IDDS in particular among the oncological community. Future research could also aim to explore the reduction in systemic opioids achieved after IDDS and how this changes over time, as well as if there are certain patient populations that experience greater benefits from IDDS. Anecdotally, during chart review we observed that there were many patients who were hospitalized on high dose IV narcotics who were then able to discharge after implantation. There were also many patients who were unable to achieve adequate pain control due to severe medication side-effects and, thus, future research could aim to quantify the presence of and changes in various side-effects such as nausea, sedation, and constipation.

CONCLUSION

Ultimately, we hope that continuing to build the body of literature in support of IDDS for cancer pain will accelerate the rate of adoption of this treatment modality for patients suffering from cancer-related pain. Our study shows significant decreases in pain scores post-IDDS implantation in a variety of cancer types, suggesting that IDDS has the potential to successfully improve cancer-related pain in a wide variety of patients. IDDS should be strongly considered for those with intractable cancer pain, as increased utilization could potentially provide improvements in both pain and quality of life for many.

REFERENCES

1. Jemal A, Ward EM, Johnson CJ et al. Annual Report to the Nation on the Status of Cancer, 1975–2014, Featuring Survival. *J Natl Cancer Inst* 2017;109:djx030–djx030.
2. Stearns L, Boortz-Marx R, Du Pen S et al. Intrathecal drug delivery for the management of cancer pain: a multidisciplinary consensus of best clinical practices. *J Support Oncol* 2005;3:399–408. [PubMed: 16350425]
3. Smith TJ, Staats PS, Deer T et al. Randomized clinical trial of an implantable drug delivery system compared with comprehensive medical management for refractory cancer pain: impact on pain, drug-related toxicity, and survival. *J Clin Oncol* 2002;20:4040–4049. [PubMed: 12351602]
4. Gough N, Miah AB, Linch M. Nonsurgical oncological management of cancer pain. *Curr Opin Support Palliat Care* 2014;8:102–111. [PubMed: 24675403]
5. Breivik H, Cherny N, Collett B et al. Cancer-related pain: a pan-European survey of prevalence, treatment, and patient attitudes. *Ann Oncol* 2009;20:1420–1433. [PubMed: 19244085]
6. van den Beuken-van Everdingen MH, de Rijke JM, Kessels AG, Schouten HC, van Kleef M, Patijn J. Prevalence of pain in patients with cancer: a systematic review of the past 40 years. *Ann Oncol* 2007;18:1437–1449. [PubMed: 17355955]
7. Kroenke K, Theobald D, Wu J, Loza JK, Carpenter JS, Tu W. The association of depression and pain with health-related quality of life, disability, and health care use in cancer patients. *J Pain Symptom Manage* 2010;40:327–341. [PubMed: 20580201]
8. Green CR, Hart-Johnson T, Loeffler DR. Cancer-related chronic pain: examining quality of life in diverse cancer survivors. *Cancer* 2011;117:1994–2003. [PubMed: 21509777]
9. Deer TR, Smith HS, Burton AW et al. Comprehensive consensus based guidelines on intrathecal drug delivery systems in the treatment of pain caused by cancer pain. *Pain Physician* 2011;14:E283–E312. [PubMed: 21587338]
10. World Health Organization. Treatment of cancer pain. Geneva, Switzerland: World Health Organization, 1997 <http://www.who.int/cancer/palliative/painladder/en/>
11. Meuser T, Pietruck C, Radbruch L, Stute P, Lehmann KA, Grond S. Symptoms during cancer pain treatment following WHO-guidelines: a longitudinal follow-up study of symptom prevalence, severity and etiology. *Pain* 2001;93:247–257. [PubMed: 11514084]

12. Lamer TJ. Treatment of cancer-related pain: when orally administered medications fail. *Mayo Clin Proc* 1994;69:473–480. [PubMed: 8170201]
13. Staats PS. Neuraxial infusion for pain control: when, why, and what to do after the implant. *Oncology (Williston Park)* 1999;13:58–62. [PubMed: 10356700]
14. Bottros MM, Christo PJ. Current perspectives on intrathecal drug delivery. *J Pain Res* 2014;7:615–626. [PubMed: 25395870]
15. Lamer TJ, Deer TR, Hayek SM. Advanced innovations for pain. *Mayo Clin Proc* 2016;91:246–258. [PubMed: 26848005]
16. Meyer R, Patel AM, Rattana SK, Quock TP, Mody SH. Prescription opioid abuse: a literature review of the clinical and economic burden in the United States. *Popul Health Manag* 2014;17:372–387. [PubMed: 25075734]
17. Vissers KC, Besse K, Wagemans M et al. 23. Pain in patients with cancer. *Pain Pract* 2011;11:453–475. [PubMed: 21679293]
18. Smith TJ, Coyne PJ, Staats PS et al. An implantable drug delivery system (IDDS) for refractory cancer pain provides sustained pain control, less drug-related toxicity, and possibly better survival compared with comprehensive medical management (CMM). *Ann Oncol* 2005;16:825–833. [PubMed: 15817596]
19. Lin CP, Lin WY, Lin FS, Lee YS, Jeng CS, Sun WZ. Efficacy of intrathecal drug delivery system for refractory cancer pain patients: a single tertiary medical center experience. *J Formos Med Assoc* 2012;111:253–257. [PubMed: 22656395]
20. Hayek SM, Deer TR, Pope JE, Panchal SJ, Patel VB. Intrathecal therapy for cancer and non-cancer pain. *Pain Physician* 2011;14:219–248. [PubMed: 21587327]
21. National Comprehensive Cancer Network. NCCN guidelines for adult cancer pain. National Comprehensive Cancer Network, 2017.
22. Engle MP, Vinh BP, Harun N, Kooyalagunta D. Infectious complications related to intrathecal drug delivery system and spinal cord stimulator system implantations at a comprehensive cancer pain center. *Pain Physician* 2013;16:251–257. [PubMed: 23703411]

Figure 1.
Mean pain score over time.