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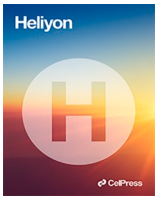

Research article

Intrathecal drug delivery systems for cancer pain: A retrospective analysis at a single tertiary medical center in China

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ABSTRACT

Objective: Intrathecal drug delivery systems (IDDS) have been clinically applied to treat refractory cancer-related pain for years. In this study, we demonstrate the current clinical practice and outcomes of IDDS for cancer pain management over a 3-year period at a single tertiary medical center in China.

Methods: Patients who received IDDS implantation for cancer-related pain from 2021 to 2023 were identified. The electronic medical records of all eligible patients were retrospectively reviewed for study data including baseline characteristics, IDDS variables and postoperative clinical outcomes.

Results: A total of 96 consecutive individuals were identified for analysis and complete follow-up information was available in 72 patients with a follow-up rate of 75 %. Patients were 49.0 % female with a mean age of 62 ± 10 years. The top five cancer types in IDDS population were lung (34.4 %), colorectal (17.7 %), pancreatic (11.5 %), breast (5.2 %) and liver (4.2 %) cancer. The median duration from cancer diagnosis to IDDS implantation was 24 months (interquartile range [IQR] 12–48 months) and from pain onset to IDDS implantation was 6 months (IQR 2–12 months). In addition, the median oral morphine equivalents (OME) daily dose was 290 mg (IQR 100–632 mg). Mean NRS was 7.5 ± 0.8 before implantation and decreased to an average of 3.0 ± 1.1 after IDDS ($p < 0.001$). Median overall survival after IDDS implantation was 3 months (IQR 2–6 months). Overall, 75 % family members of cancer patients were satisfied with IDDS in relieving cancer pain.

Conclusion: IDDS therapy is a valuable option for patients suffering from cancer pain. More and more cancer pain patients receive IDDS to treat pain during the 3-year study period.

1. Introduction

Cancer has become a major global public health challenge, and the incidence and mortality of cancer is rapidly increasing worldwide. According to Global Cancer Statistics 2020, there were 19.3 million new cancer cases and almost 10.0 million cancer deaths in 2020, and the number of cancer cases is expected to be 28.4 million in 2040 [1]. Pain is still one of prevalent sufferings of patients with cancer. The prevalence of cancer pain has been reported to be 39.3 % after curative treatment; 55.0 % during anticancer

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treatment; and 66.4 % in advanced, metastatic, or terminal disease, with 38.0 % of all patients classifying it as moderate to severe pain [2].

There currently exists various therapeutic strategies for cancer pain including medications and interventional treatments. From 1986, the World Health Organization (WHO) analgesic ladder has been used as guidance in the pharmaceutical cancer pain management, with opioids being considered as the mainstay [3]. However, there are still many cases failing to get adequate control of pain from pharmacological therapy alone or suffering from intolerable side effects [4]. Thus, interventional treatments should be adopted as part of comprehensive therapy in patients with intractable cancer pain to maximize analgesic efficacy and minimize adverse effects [5].

Nowadays, interventional procedures include peripheral nerve blockade, neuro-destructive techniques, neurostimulation device use, and intrathecal drug delivery systems (IDDS). IDDS has been increasingly recommended and applied to treat patients with refractory cancer pain worldwide [6]. To our knowledge, however, the current clinical practice pattern and outcomes of IDDS for cancer pain in China has not been well described. In this retrospective study, we aimed to demonstrate and analyze the IDDS use for cancer pain management over a 3-year period in a single tertiary medical center.

2. Materials and methods

This retrospective and observational study was conducted after obtaining Ethics Institutional Review Board approval from China-Japan Friendship Hospital and informed consent was waived for the design of this study (2024-KY-076).

We reviewed the records of patients who underwent IDDS implantation with the SynchroMed II Infusion System (Medtronic, Inc, Minneapolis, MN) for cancer-related pain from 2021 to 2023 in our center. In our institute, we only have one type of IDDS, namely the SynchroMed II Infusion System. Exclusion criteria included patients with missing data for the studied parameters and with an intrathecal pump implanted for nonmalignant pain.

Studied data were collected by retrospectively reviewing the electronic medical records of all eligible patients. The collected parameters consisted of baseline characteristics, IDDS variables, and postoperative clinical outcomes.

Baseline characteristics included age, gender, body mass index (BMI), basic activity of daily living (ADL) score, physical condition, type of cancer, prior cancer treatment (operation, chemoradiotherapy and immunotherapy), oral morphine equivalent (OME) daily dose (including oral, transdermal and parenteral opioid medications), number of adjunctive medications, cancer duration (from cancer diagnosis to IDDS implantation), pain duration (from pain onset to IDDS implantation), pain location, baseline pain score using numerical rating scale (NRS), insurance status, and total hospital charge.

IDDS variables contained times of intrathecal screening trial (ITT), type and initial dose of drugs used in ITT, operation time (from initial incision to wound closure), insertion level, location of catheter tip, type and initial dose of drugs delivered in IDDS.

Postoperative clinical outcomes included total length of hospitalization (from patient admission to discharge), postoperative length of stay (from IDDS implantation to patient discharge or in-hospital death), postoperative complications (including infections, pump-related complications and catheter-related complications), pain score, overall survival time (from IDDS implantation to patient either death or alive at the end of last telephone follow-up) and overall satisfaction with IDDS by family members. The last telephone follow-up was on March 20, 2024.

Table 1
Patient-related characteristics.

Characteristics	Total (n = 96)
Age (years)	62 ± 10
Gender (female/male)	47/49 (49 %/51 %)
BMI (kg/m^2)	20.7 ± 3.1
ADL score at surgery	67 ± 24
Cancer type (top 3)	
Lung	33 (34.4 %)
Colorectal	17 (17.7 %)
Pancreas	11 (11.5 %)
Cancer metastasis (top 3)	
Bone	38 (39.6 %)
Live	18 (18.8 %)
Lung	8 (8.3 %)
Prior cancer treatment	
Surgery	49 (51.0 %)
Chemoradiotherapy	64 (66.7 %)
Immunotherapy	30 (31.3 %)
Cancer duration (month)	24 (12–48)
Pain duration (month)	6 (2–12)
Oral morphine equivalent (mg/d)	290 (100–633)

Values are expressed as mean ± standard deviation, median (IQR) or number of patients (n, %).
Abbreviations: SD, standard deviation; IQR, interquartile range; BMI, body mass index; ADL, activity of daily living.

Continuous variables were presented as mean ± standard deviation (SD) or median with interquartile range (IQR). Categorical variables were reported as frequency and percentage (n, %). Paired samples *t*-test was performed on the differences of pain scores before and after IDDS implantation. Patient survival was estimated using Kaplan–Meier survival analysis. All statistical analyses were performed using SPSS software (Statistical Package for the Social Sciences, version 22.0, SPSS Inc, Chicago, IL), and p values < 0.05 were considered statistically significant.

3. Results

3.1. Patient demographic characteristics

From January 2021 to December 2023, a total of 96 consecutive patients who received IDDS implantation to treat cancer pain were identified for analysis in this study. The IDDS population consisted of 49 men (51.0 %) and 47 women (49.0 %) with a mean age of 62 ± 10 years. Twenty-nine patients (30.2 %) were underweighted, with BMI ranging from 14.3 to 29.4 kg/m^2 (mean 20.7 ± 3.1 kg/m^2). At the time of IDDS implantation, many patients were in poor physical condition with a mean ADL score of 67 ± 24 points. Besides, 53 patients (55.2 %) were admitted by wheelchair or cart, 37 patients (38.5 %) were in low performance status with ADL below 60 points, and 23 patients (24.0 %) developed pressure sores. Twenty-eight patients (29.2 %) had at least one skin compromising indwelling line, such as gastrostomy, enterostomy, indwelling urethral catheter, gall bladder/abdominal/thoracic drainage tube.

On average, the length of total hospital stay was 11 ± 5 days and the mean time from IDDS implantation to discharge was 6 ± 3 days. Most patients had basic medical insurance and the mean cost of total hospital admission was ¥152,084 ± 10,395. After Medicare reimbursement, patients pay ¥45,108 ± 28,401 at their own expense. The number of patients receiving IDDS therapy in 2021, 2022 and 2023 was 27 (28.1 %), 18 (18.8 %) and 51 (53.1 %), respectively. Patient-related Characteristics are demonstrated in Table 1.

3.2. Tumor information

The top five cancer types in patients undergoing IDDS were lung (34.4 %), colorectal (17.7 %), pancreatic (11.5 %), breast (5.2 %) and liver (4.2 %) cancer. The median (IQR) duration from cancer diagnosis to IDDS implant was 24 months (12–48 months). Of these patients, more than half of the patients (62.5 %) had advanced cancer with metastasis and 39.6 % of patients had bone metastases. Most patients (88.5 %) were already treated with some form of antineoplastic therapy before IDDS implantation, including 64 (66.7 %) with chemoradiotherapy, 30 (31.3 %) with immunotherapy, and 49 (51.0 %) with operation.

3.3. Basic pain information

The pain locations in the study population included lumbosacral region (41.7 %), abdomen (31.3 %), back (27.1 %), lower extremity (19.8 %), perineal region (7.3 %), chest (7.3 %), head and neck (5.2 %), and upper extremity (2.1 %). Medical history data indicated that the median (IQR) duration from pain onset to IDDS implantation was 6 months (2–12 months). In 12.5 % of patients, the onset of pain preceded the detection of cancer.

Among these patients, 66 (68.8 %) were taking a systemic opioid. High doses of oral morphine equivalents (OME) were consumed by patients prior to IDDS implantation, with a median (IQR) OME daily dose of 290 mg (100–633 mg). Forty-one patients (42.7 %) required an OME greater than 200 mg and 23 (24.0 %) required greater than 500 mg. Thirty-one patients (32.3 %) received at least one adjuvant drug of NSAIDS, anticonvulsants, or antidepressants, as clinically indicated. Seven patients (7.3 %) had been treated previously with other procedures such as radiofrequency ablation to relieve cancer pain before IDDS.

Inadequate pain control of previous treatment was the primary reason for IDDS implantation, occurring in 90 cases (93.8 %). Intolerance to the side-effects of opioids were cited in 6 cases (6.3 %), such as intractable nausea and vomiting, severe urine retention.

3.4. Screening trial

As for intrathecal screening trial (ITT), 68 patients (70.8 %) received once, 11 patients (11.5 %) received twice, and 17 patients (17.7 %) did not undergo the procedure. The top two drugs used in ITT were morphine (44.8 %) and hydromorphone (34.4 %). The mean doses of ITT were 0.18 ± 0.10 mg for morphine and 0.03 ± 0.02 mg for hydromorphone.

3.5. Surgical indicators

The mean surgical duration was 2.34 ± 0.68 h. As for insertion level, most cases were punctured at L2/3 and L3/4 level (57.3 % and 31.3 %, respectively) and catheter was moved upward in 94.8 % of cases. Patients were divided into 3 groups based on IDDS catheter tip location: T1-T5, T6-T9 and below T10. Most catheter tips (64.6 %) were placed in the thoracic spine between T6-T9 and mainly in T6 (19.8 %) based on pain location.

Patients began IDDS with morphine for 61 patients (63.5 %), hydromorphone for 25 patients (26.0 %), bupivacaine for 1 patient (1.0 %), a combination of bupivacaine and morphine for 9 patients (9.5 %). The mean initial dose of these analgesics are as follows: morphine 1.07 ± 1.05 mg/d and hydromorphone 0.16 ± 0.13 mg/d. In our center, the initial dose was not standardized. It depended on patients' OME dose before implantation, side effects, and physicians' clinical experience. Operation-related Values are indicated in Table 2.

3.6. Complications

Among the 96 patients, 12 (12.5 %) patients experienced postdural puncture headache, 8 (8.3 %) had a fever postoperatively, 3 (3.13 %) reported urine retention and constipation in the first 5 days, and 1 (1.04 %) died the day after surgery. The in-hospital mortality was 1.04 % among the recipients of IDDS. During the entire follow up, we observed 1 case of poor wound healing due to severe wasting and malnutrition, and IDDS (pump and catheter) was removed beyond 10 months of implantation.

3.7. Pain follow-up and patient survival

Among 96 patients, 24 were excluded due to perioperative death, removal of IDDS (pump and catheter) due to poor wound healing, loss to or refusal to follow up. Finally, 72 patients were included with a follow-up rate of 75 %.

Compared with preimplantation, IDDS was associated with pain relief significantly. Mean NRS was 7.5 ± 0.8 before implantation and decreased to an average of 3.0 ± 1.1 after IDDS ($p < 0.001$). Twenty-three patients (31.9 %) stopped previous systemic opioid therapy and 37 patients (51.4 %) continued to use less than 100 mg OME daily after IDDS. Overall, 75 % family members of 72 cancer patients were satisfied with IDDS in relieving cancer pain. Eighteen (25 %) were unsatisfied due to poor pain control, inconvenience by frequent pump refilling and short survival time after implantation.

Fifty-six patients died after discharge during the study period and all deaths were due to disease-related causes. Median (IQR) overall survival after IDDS implantation was 3 months (2–6 months). Data for clinical follow-up and patient outcomes are shown in Table 3. Survival curve is presented in Fig. 1.

4. Discussion

This is only an observational study mainly analyzing the clinical experience of patients who received IDDS implantation to treat cancer pain in a single pain management center in China.

IDDS has been applied clinically to treat refractory cancer-related pain for years. Lot of literature have demonstrated that it likely reduces pain intensity and decreases the use of systemic opioids and increases health-related quality of life and may also improve functional outcomes in patients with cancer pain [7–11]. However, it appears to be underused clinically in China.

The Department of Pain Management in our hospital is the earliest pain department in China, and it took the lead in applying IDDS

Table 2
Operation-related values.

Values	Total (n = 96)
Times of ITT	
0	17 (17.7 %)
1	68 (70.8 %)
2	11 (11.5 %)
Drugs for ITT	
Morphine	43 (44.8 %)
Hydromorphone	33 (34.4 %)
Bupivacaine	3 (3.1 %)
Dose of morphine for ITT (mg)	0.18 ± 0.10
Dose of hydromorphone for ITT (mg)	0.03 ± 0.02
Insertion level	
L2/3	55 (57.3 %)
L3/4	30 (31.3 %)
Other	11 (11.4 %)
Location of IDDS catheter tip	
T1-T5	3 (3.1 %)
T6-T9	62 (64.6 %)
Below T10	31 (32.3 %)
Drugs for IDDS	
Morphine	61 (63.5 %)
Hydromorphone	25 (26.0 %)
Bupivacaine	1 (1.0 %)
Combination of bupivacaine and morphine	9 (9.5 %)
Surgical duration (hour)	2.34 ± 0.68
Initial dose of morphine for IDDS (mg)	1.07 ± 1.05
Initial dose of hydromorphone for IDDS (mg)	0.16 ± 0.13
Total length of hospital stay (day)	11 ± 5
Cost of total hospital admission (¥)	152,084 ± 10,395
Cost at patients' own expense (¥)	45,108 ± 28,401

Values are expressed as mean ± standard deviation, median (IQR) or number of patients (n, %).

Abbreviations: SD, standard deviation; IQR, interquartile range; ITT, intrathecal screening trial; IDDS, Intrathecal drug delivery systems.

Table 3
Data for clinical follow-up and patient outcomes.

Data	Total (n = 72)
NRS at surgery	7.5 ± 0.8
NRS at follow-up	3.0 ± 1.1
Satisfaction with IDDS	54 (75 %)
Months from implant to death/last visit	3 (2–6)

Values are expressed as mean ± standard deviation, median (IQR) or number of patients (n, %).
Abbreviations: SD, standard deviation; IQR, interquartile range; NRS, numerical rating scale; IDDS, intrathecal drug delivery systems.

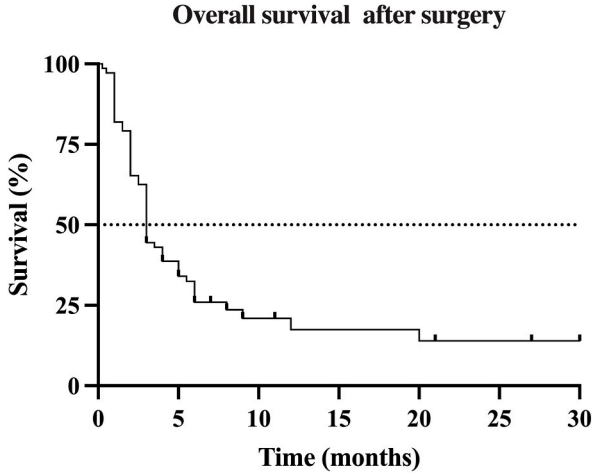

Fig. 1. Overall survival from IDDS implantation. IDDS: intrathecal drug delivery system.

to treating cancer pain in China. With the improvement of living standard, more and more cancer pain patients have now received this procedure to treat pain. In our center, the overall trend of IDDS implantation increased year by year during the 3-year study period.

IDDS is one of interventional analgesia treatments which delivers continuously accurate and small doses of analgesic drugs in the intrathecal space [12]. It relieves pain by using much smaller doses than oral or other routes [13]. Although neuromodulation literature has suggested that it should not be used as a salvage therapy after failure of systemic high-dose opioid-based medicines [14], dissatisfaction with the efficacy of previous treatment was still the main reason (93.8 %) for IDDS implantation in our center and most patients had experienced chronic pain (lasting for 6 months on average) taking a high dose of systemic opioid (median OME daily dose of 290 mg) before IDDS implantation. Other studies reported similar OME doses (240–320 mg/d) taken by patients prior to IDDS [15–18].

In our institute, solid tumors were mainly the most common cancer type in patients receiving IDDS with lung (34.4 %), colorectal (17.7 %), pancreatic (11.5 %), breast (5.2 %) and liver (4.2 %) cancer predominating, which were similar to those reported in other literature [16,19,20]. Besides, a large percentage of patients (62.5 %) had advanced cancer with metastasis with bone metastasis in 39.6 % of patients, which was higher than that of other study [19]. Our study showed that the top three pain locations in patients undergoing IDDS included lumbosacral region (41.7 %), abdomen (31.3 %) and back (27.1 %). Thus, it is not difficult to understand that catheter tips of IDDS were mainly placed in the thoracic spine between T6-T9 (64.6 %) in our center.

Intrathecal screening trial is not a mandatory procedure before IDDS implantation, but it was performed in 82.3 % patients in our center. Although many analgesics are approved and recommended for IDDS [21,22], the medications used in all patients included in the analysis were limited to morphine, hydromorphone, and bupivacaine, alone or in combination. In our center, morphine was still the most common IDDS-infused medications; the clinical application of hydromorphone has gradually increased with its approval; and bupivacaine was relatively less used in clinical practice and mainly used in combination.

Analysis of both baseline and follow-up data, our study has shown that IDDS is an effective treatment for patients suffering from cancer pain. Following IDDS implantation, mean NRS decreased from 7.5 ± 0.8 to 3.0 ± 1.1 ($p < 0.001$). Systemic opioid was stopped or used less after IDDS in 83.3 % patients, with an overall satisfaction rate of 75 % in family members. Additionally, our study showed that the median overall survival after IDDS implantation was 3 months, which is in accordance with several previous studies [9,18].

Several limitations should be considered when interpreting our study results. First, our study is monocentric and observational. Data were collected mainly from electronic medical records and not all parameters of interest were included in many cases. Thus, the results may not be generalized to all centers that perform IDDS implantations given the retrospective design. Second, recall bias cannot be ignored because our postoperative follow-up was completed mainly by family members via telephone call as most patients died

during follow-up. Third, we do not have accurate data on change in systemic opioid medication use, associated complications with IDDS, the details of performance status, the change of dose of opioids after IDDS implantation and postoperative quality of life scores. Thus, we did not assess these outcomes as they were uncertain or difficult to achieve.

5. Conclusion

IDDS is an effective and safe treatment option for patients suffering from cancer pain in our study population. With the improvement of living standard, more and more cancer pain patients receive IDDS to relieve pain during the 3-year study period.

Data availability statement

Data included in article have not been deposited into a publicly available repository and they will be made available on request.

Ethics and consent statement

This study was reviewed and approved by Ethics Institutional Review Board of China-Japan Friendship Hospital with the approval number 2024-KY-076, dated 2024/3/11 and informed consent was waived for the design of this study.

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CRediT authorship contribution statement

Wen Wang: Writing – original draft, Data curation, Conceptualization. **Qing Shi:** Visualization, Formal analysis, Data curation. **Yanting Cao:** Visualization, Formal analysis, Data curation. **Bifa Fan:** Writing – review & editing, Data curation. **Yang Yang:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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