Clinical Case Report

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Palliative care with cervical intrathecal infusion and external pump for a late-stage cancer patient with refractory pain

A case report

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Abstract

Rationale: Intrathecal therapy, with a low complication rate, has become an alternative to standard pain management for treatment of neuropathic cancer pain.

Patient concerns: Here, we reported a late-stage cancer patient with intractable neuropathic pain in his right neck, shoulder, and upper limb.

Diagnoses: The pain started 2 years ago when the patient was diagnosed as squamous cell carcinoma with metastasis to right supraclavicular lymph nodes.

Interventions: Cervical intrathecal infusion of morphine and bupivacaine with patient control analgesia by external pump was performed. The intrathecal catheter was located at the level of C6 vertebra. The initial concentration of bupivacaine and morphine were both 1 mg/mL with infusion rate of 0.3 mL/h and bolus of 0.3 mL. Subsequently, the concentrations increased to 2 mg/mL (bupivacaine) and 1.33 mg/mL (morphine), with infusion rate to 0.6 mL/h and bolus to 0.5 ml.

Outcomes: The pain intensity decreased from numerical rating scale 6 to 7 to 2 to 3 at rest, and from 10 to 5 to 6 of breakthrough pain.

Lessons: In conclusion, cervical intrathecal infusion requires low concentration but high doses of bupivacaine and morphine, which is safe and effective in cancer patients with refractory pain and short life expectancy.

Abbreviations: CSF = cerebrospinal fluid, DSA = digital subtraction angiography, NRS = numerical rating scale, PCA = patient-controlled analgesia.

Keywords: bupivacaine, cancer pain, cervical, intrathecal, opioid, terminal life

1. Introduction

Pain is prevalent in patients with advanced cancer.[1] The World Health Organization has put forward 3 steps in treating cancer pain,[2] but there are still about 5% to 15% of patients who have failed pain relief because of refractory pain and intolerable side-effects of systemic opioids.[3] Intrathecal therapy has become an alternative to standard medical management for pain reduction during cancer pain therapy.[4] The Polyanalgesic Consensus Conference panel of experts convened in 2000, 2003, 2007, 2012, and 2016 to make recommendations on use of intrathecal analgesics based on preclinical trials and clinical experiences.[5,6] Intrathecal therapy delivers medication directly into intrathecal space of the spinal column via an indwelling catheter connected to an implanted reservoir, which is controlled by a programmable pump and may be implanted or external.[7–9] But the use of implantable pumps is considered costly in terminal patients.[10] In a recent study from the Cleveland Clinic, intrathecal patient-controlled analgesia (PCA) was found to be cost-effective.[11] Apart from, the intrathecal PCA results in better patient satisfaction.[12] The tip of the catheter is usually placed near the point that produces the worst pain.[13] However, whether the catheter tip can be located at the level of cervical vertebra is rarely reported.

Herein, we described a case of terminal cancer patient with intractable neuropathic pain who was treated with intrathecal PCA with external pump. The catheter tip was located at the 6th cervical vertebra.

2. Case report

A 73-year-old Chinese male patient was admitted to our pain ward with unbearable pain of right neck, shoulder, and upper limb for 6 months. The pain started 2 years ago when the patient

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was diagnosed as squamous cell carcinoma with metastasis to right supraclavicular lymph nodes. However, the primary tumor was not identified. He received 2 cycles of systemic chemotherapy and 2 rounds of local radiation therapy. The swelling of the right supraclavicular lymph nodes subsided but the pain remained. He was treated with the 3-step pain control method recommended by the World Health Organization for 1 and a half years. However, the pain exaggerated with electric shock radiating to the right upper extremity. He experienced insomnia and was forced on left decubitus or sitting position with severely limited motion. He had normal liver function and renal function. No significant abnormality was shown in cardiopulmonary function and coagulation test. Medications used for pain management included oxycodone 560 mg [oral, bis in die (bid)] and morphine 150 mg (oral, bid), and morphine 10 mg (intramuscular injection, 5–6 times a day). He rated his pain as 6 to 7 on numerical rating scale (NRS) at rest and 10 of breakthrough pain, which happened frequently. His main purpose was to alleviate pain and improve life quality. He refused conservative medical management and his life expectancy was less than 6 months. Thus, after an overall consideration, we decided to implant an intrathecal catheter with an external pump.

For implantation of the intrathecal catheter, the patient was positioned in left decubitus position. The level L3 to L4 was selected for the introduction of the Tuohy needle to the subarachnoid space. The 22-gauge catheter advanced slowly into subarachnoid space under the guidance of digital subtraction angiography (DSA). The catheter position was confirmed by free flow of cerebrospinal fluid (CSF) on radiographic contrast imaging. The tip of the catheter was located at the level of C6 vertebra (Fig. 1). The catheter was connected to a port approximately 1 cm below the skin surface. An external electronic pump was connected to the port through an en-Winged Surecan needle. A 100-mL reservoir of the external electronic pump was desired and filled with bupivacaine and morphine. The concentrations of bupivacaine and morphine were both 1 mg/mL with infusion rate of 0.3 mL/h and initial bolus of 0.3 mL, and locking-time was 30 minutes. Only morphine (oral 150 mg, twice a day) continued after intrathecal therapy. In the first 24 hours, 2 boluses were used apart from continuous intrathecal infusion. The patient rated the pain NRS 2 to 3 at rest and NRS 5 to 6 of breakthrough pain, which could be managed by a bolus. On the 4th day, he had a severe breakthrough pain rating NRS 8 that could not be alleviated even by 3 boluses. Then parecoxib sodium 40 mg was given by intravenous injection and his pain was controlled. The concentration of bupivacaine increased to 1.25 mg/mL on the same day. From then on, the breakthrough pain happened occasionally, which could be managed by 1 single bolus. He could lie on his back and sleep 3 to 5 hours at night. He was discharged at the 8th day after the procedure. At 10th day, he stopped oral morphine by himself and suffered systemic discomfort and irritation a few hours later, which was considered as withdrawal effect of rapid reduce of opioid dose. A higher dose of oral morphine was refused by him. The concentration was adjusted to morphine 1.2 mg/mL and bupivacaine 1.5 mg/mL on the 12th day. The concentrations were maintained till the 22nd day, and then with the progression of his cancer, the concentrations were increased to morphine 1.33 mg/mL and bupivacaine 1.75 mg/mL, with infusion rate at 0.6 mL/h and bolus 0.5 mL. At 70th day, the concentration of bupivacaine was increased to 2 mg/mL to treat even worsen pain and the concentration of morphine remained 1.33 mg/mL. The acceptable pain management according to the patient was NRS 2 to 3 at rest and NRS 5 to 6 of breakthrough pain, which could be controlled by 1 bolus. When the pain score was larger than the acceptable pain score, the concentration of the drugs, the infusion rate, and the dose of a bolus were adjusted. After every adjustment, he was satisfied with the pain management. The pain medication regimens are shown in Table 1.

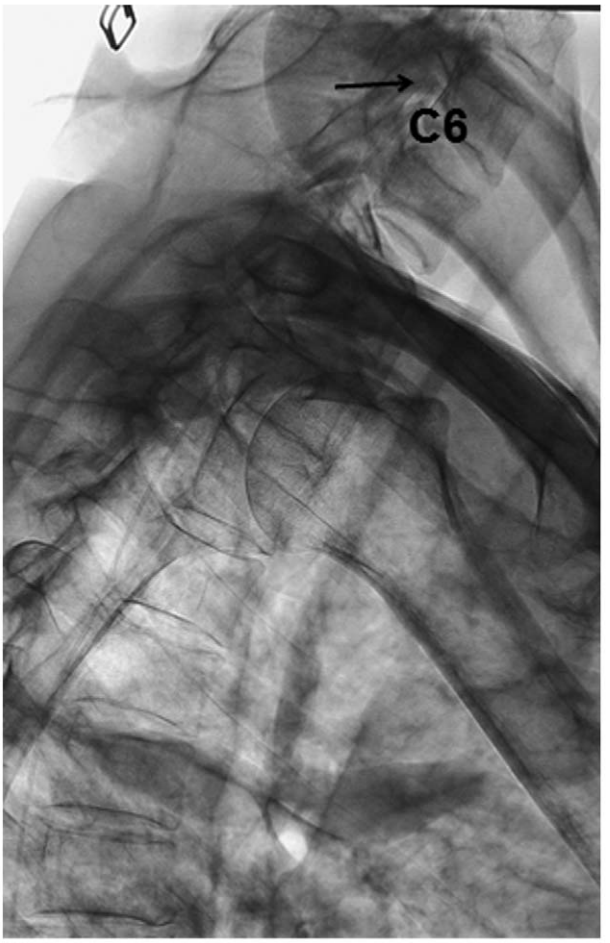

Figure 1. Position of intrathecal catheter (arrow). The tip was located at the C6 vertebra on digital subtraction angiography image.

The needle was changed twice a week and the reservoir was changed whenever needed by a trained nurse to avoid infection. The patient died of respiratory and circulatory failure at 80th day at home. No drug-related complications occurred during intrathecal analgesia. The patient and the family were satisfied. Prior written and informed consent were obtained from the patient's family and the study was approved by the ethics review board of Weihai Municipal Hospital.

3. Discussion

Pain is the most prevalent symptom in cancer patients.[14,15] With the progression of cancer and the tumor invading the nerve, organ, and bone, there will be severe pain.[16] The treatment to cancer rather than the cancer itself could cause chronic pain in cancer survivors.[17,18] Radiation therapy, chemotherapy, and operation can cause long-term neuropathic pain.[15] In this patient, the metastasis of cancer and radiation therapy performed repeatedly in the supraclavicular lymph node resulted in nerve

Table 1

Medication regimens of intrathecal therapy.

Time after intrathecal therapy		Day 1	Day 5	Day 15	Day 30	Day 70
Intrathecal morphine	Concentration (mg/mL)	1	1	1.2	1.33	1.33
	Dosage (mg/d)	7.8	8.7	10.44	21.81	21.81
Intrathecal bupivacaine	Concentration (mg/mL)	1	1.25	1.5	1.75	2
	Dosage (mg/d)	7.8	10.88	13.05	28.7	32.8
	Infusion rate (ml/h)	0.3	0.3	0.3	0.6	0.6
	Bolus (mL)	0.3	0.3	0.3	0.5	0.5
	Times of bolus	2	5	5	4	4

injuries, causing neuropathic pain. The patient was not sensitive to escalated sequential dosage of strong systemic opioids as his pain developed. Intrathecal therapy is widely used to treat refractory cancer pain, which is better than systemic therapy in that drugs are delivered to receptor sites in the dorsal horn of the spinal cord.[19] Morphine acts directly on pain processing center in the spinal cord, therefore, the dose required is lower and the side effects are fewer.[20]

For neuropathic pain, the first-line intrathecal therapy contains morphine alone or in combination with the local anesthetic bupivacaine.[5] Morphine is an agonist of μ-opioid receptor in the dorsal horn region of the spinal cord. Morphine sulfate is hydrophilic so that it spreads quickly and widely in the CSF.[5] The effect of bupivacaine is via blocking the Na^+ channels of neuronal tissue and disrupting pain transmission[21]. Intrathecal infusion of bupivacaine could block the sensory conduction to get better analgesia.[22] The high lipid solubility of bupivacaine limits its intrathecal spread and highlights the need to place the catheter in the posterior intrathecal space.[23] Continuous intrathecal therapy with low flow-rate infusion shows that drug distribution in the CSF and uptake in the spinal cord are limited to a few centimeters around the tip of the catheter,[24,25] and the catheter should be placed at a spinal location congruent with the primary site of pain origin.[8,26] Therefore, in this case, the catheter tip was located at the 6th cervical vertebra.

The recommended starting dosage of intrathecal medications for long-term intrathecal therapy is morphine 0.1 to 0.5 mg/d and bupivacaine 0.01 to 4 mg/d.[6] In this case, the dose of intrathecal morphine used at first was 7.8 mg/d, which was much more than the recommendation. This is because the morphine-equivalent oral dose/d was about 2130 mg before intrathecal therapy and the dose of intrathecal morphine was about 1/300th of the oral dose.[27,28] The dose of intrathecal bupivacaine was 7.8 mg/d which was more than 4 mg/d. To avoid the side-effect, the concentration of bupivacaine was low. The application of bupivacaine for intrathecal therapy may have common adverse effects such as motor weakness and hypotension.[5,29] Thus, we chose low concentration of 1 mg/mL at the beginning and increased to 2 mg/mL step by step, with the infusion rate ranging from 0.3 to 0.6 mL/h. Therefore, the patient gradually adapted to the dose. It is not recommended to abruptly stop systemic dose of morphine to prevent withdrawal symptoms.[27] After intrathecal therapy, we advised the patient to take morphine orally. However, at the 10th day he stopped oral morphine by himself because he felt his pain was controlled well. We had to increase the concentration of both drugs to control pain and alleviate opioid abstinence. The recommended maximum intrathecal concentration of morphine is 20 mg/mL and that of bupivacaine is 30 mg/mL. The recommended maximum dose/d is morphine of 15 mg and bupivacaine of 15 to 20 mg to reduce the risk of granuloma formation and minimize complications, but the doses of morphine and bupivacaine may exceed this recommendation in end-of-life care and complicated cases as determined by medical necessity.[6,30] In this case, the maximum doses/d of morphine (21.81 mg/d) and bupivacaine (32.8 mg/d) were both larger than the recommendations, but the concentration of both drugs were low. The common side-effects related to morphine and bupivacaine were not observed.

Fully implantable pump is suitable for long-term use.[31] Successful clinical implementation of the implantable pump requires significant training of the physicians.[32]Additionally, the implantable pumps are not cost-effective in patients with short life expectancy.[10] An external drug infusion is used as an alternative approach in cancer patients with a short life expectancy.[33,34] Thus, an external pump was used in the case of this study.

It has been reported that better patient satisfaction in cancer-related pain could be acquired by intrathecal PCA with bolus dosing.[35] PCA system allows the patient to administer boluses of medication by himself in response to breakthrough pain during use of a continuous pump system.[11] The external electronic pump offers continuous medication infusion. If the cancer pain is not controlled sufficiently in the early days, we could raise the concentration, dosage, and infusion rate of morphine and bupivacaine. It is a more convenient and inexpensive way to add morphine and bupivacaine into the reservoir or change another reservoir.

The catheter must be advanced slowly into cervical subarachnoid space under the guidance of DSA to avoid nerve injuries. The trained nurse changed the port needle and sterilized the catheter insertion site twice a week carefully to avoid infection.

In conclusion, cervical intrathecal infusion with high dose of morphine and bupivacaine at a low concentration by external pump with PCA is an effective and safe way to alleviate cancer pain in patients with refractory cancer pain at the terminal life with few adverse effects. The life quality of the patient was improved.

References

[1] Bruel BM, Burton AW. Intrathecal therapy for cancer-related pain. Pain Med 2016;17:2404–21.
[2] World Health Organization Expert Committee. Cancer pain relief and palliative care. World Health Organization Technical Report Series. 1990; 804:1-73
[3] Mercadante S, Intravaia G, Villari P, et al. Intrathecal treatment in cancer patients unresponsive to multiple trials of systemic opioids. Clin J Pain 2007;23:793–8.
[4] Singh V, Manchikanti L, Benyamin RM, et al. Percutaneous lumbar laser disc decompression: a systematic review of current evidence. Pain Physician 2009;12:573–88.
[5] Deer TR, Prager J, Levy R, et al. Polyanalgesic consensus conference 2012: recommendations for the management of pain by intrathecal (intraspinal) drug delivery: report of an interdisciplinary expert panel. Neuromodulation 2012;15:436–66.

[6] Deer TR, Pope JE, Hayek SM, et al. The Polyanalgesic consensus conference (PACC): recommendations on intrathecal drug infusion systems best practices and guidelines. Neuromodulation 2017;20:96–132.
[7] Hayek SM, Deer TR, Pope JE, et al. Intrathecal therapy for cancer and non-cancer pain. Pain Physician 2011;14:219–48.
[8] Pope JE, Deer TR. Intrathecal drug delivery for pain: a clinical guide and future directions. Pain Manag 2015;5:175–83.
[9] Bottros MM, Christo PJ. Current perspectives on intrathecal drug delivery. J Pain Res 2014;7:615–26.
[10] Hassenbusch SJ, Paice JA, Patt RB, et al. Clinical realities and economic considerations: economics of intrathecal therapy. J Pain Symp Manag 1997;14:S36–48.
[11] Brogan SE, Winter NB, Okifuji A. Prospective observational study of patient-controlled intrathecal analgesia: impact on cancer-associated symptoms, breakthrough pain control and patient satisfaction. Reg Anes Pain Med 2015;40:369–75.
[12] Perruchoud C, Eldabe S, Durrer A, et al. Effects of flow rate modifications on reported analgesia and quality of life in chronic pain patients treated with continuous intrathecal drug therapy. Pain Med 2011;12:571–6.
[13] Baker L, Balls J, Regnard C, et al. Cervical intrathecal analgesia for head and neck/upper limb cancer pain: six case reports. Palliat Med 2007; 21:543–5.
[14] Westerling D. Pain and other symptoms in cancer survivors. J Pain Palliat Care Pharmacother 2014;28:160–3.
[15] Smith EM, Bridges CM, Kanzawa G, et al. Cancer treatment-related neuropathic pain syndromes-epidemiology and treatment: an update. Curr Pain Headache Rep 2014;18:459.
[16] Karver SB, Berger JH. The challenges of treating patients with cancer pain. J Support Oncol 2010;8:239–40.
[17] Glare PA, Davies PS, Finlay E, et al. Pain in cancer survivors. J Clin Oncol 2014;32:1739–47.
[18] Paice JA. Chronic treatment-related pain in cancer survivors. Pain 2011;152:S84–9.
[19] Heittiarachchi HD, Hsu Y, Harris TJ, et al. The effect of pulsatile flow on intrathecal drug delivery in the spinal canal. Ann Biomed Eng 2011;39:2592–602.
[20] Howard S, Timothy R, Peter S, et al. Intrathecal drug delivery. Pain physician 2008;11:S89–104.
[21] Abdolmohammadi S, Hétu PO, Néron A, et al. Efficacy of an intrathecal multidrug infusion for pain control in older adults and in end-stage malignancies: a report of three cases. Pain Res Manag 2015;20:118–22.
[22] Deer TR, Serafini M, Buchser E, et al. Intrathecal bupivacaine for chronic pain: a review of current knowledge. Neuromodulation 2002;5: 196–207.
[23] Bernards CM. Cerebrospinal fluid and spinal cord distribution of baclofen and bupivacaine during slow intrathecal infusion in pigs. Anesthesiology 2006;105:169–78.
[24] Flack SH, Bernards CM. Cerebrospinal fluid and spinal cord distribution of hyperbaric bupivacaine and baclofen during slow intrathecal infusion in pigs. Anesthesiology 2010;112:165–73.
[25] Flack SH, Anderson CM, Bernards C. Morphine distribution in the spinal cord after chronic infusion in pigs. Anesth Analg 2011;112:460–4.
[26] Gulati A, Puttanniah V, Hung J, et al. Considerations for evaluating the use of intrathecal drug delivery in the oncologic patient. Curr Pain Headache Rep 2014;18:391.
[27] Krames ES. Intrathecal infusional therapies for intractable pain: patient management guidelines. J Pain Symptom Manage 1993;8:36–46.
[28] 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: 825–33.
[29] Brogan S, Junkins S. Intervention therapies for the management of cancer pain. J Support Oncol 2010;8:52–9.
[30] Fujii T, Nagaro T, Tsubota S, et al. Case reports: management of intractable upper extremity pain with continuous subarachnoid block at the low cervical level without impairment of upper extremity function. Anesth Analg 2010;110:1721–4.
[31] Bhatia G, Lau ME, Koury KM, et al. Intrathecal drug delivery(ITDD) systems for cancer pain. Version 4 F1000Res 2013;2:96.
[32] Wilkes D. Programmable intrathecal pumps for the management of chronic pain: recommendations for improved efficiency. J Pain Res 2014;7:571–7.
[33] Patel VB, Manchikanti L, Singh V, et al. Systematic review of intrathecal infusion systems for long-term management of chronic non-cancer pain. Pain Physician 2009;12:345–60.
[34] Manchikanti L, Boswell MV, Datta S, et al. Comprehensive review of therapeutic interventions in managing chronic spinal pain. Pain Physician 2009;12:E123–98.
[35] Peruchoud C, Eldabe S, Durrer A, et al. Effects of flow rate modifications on reported analgesia and quality of life in chronic pain patients treated with continuous intrathecal drug therapy. Pain Med 2011;12:571–6.