—Case Reports—

A Case of Cancer Pain Management by Long-Term Intrathecal PCA

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Abstract

Titration of oral or intravenous medication is the preferred method of pain management for most patients with cancer pain. However, some patients experience insufficient pain relief or considerable adverse effects from systemic opioids. For these reasons, the control of severe cancer pain continues to present a variety of challenges to clinicians. We report our experience of successfully managing cancer pain in a patient by means of long-term intrathecal administration of morphine, bupivacaine, and racemic ketamine via a patient-controlled delivery system. This therapy reduced the patient's nausea, vomiting, and somnolence, led to early hospital discharge, and increased her level of daily activity. There were no signs of motor paralysis, psychomimetic alteration, neurological dysfunction, or infection related to the intrathecal route during treatment. Intrathecal therapy is an effective treatment in terminally ill patients.

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Key words: intrathecal therapy, cancer pain, patient controlled analgesia, opioid, ketamine

Introduction

It has been suggested that about 90% of cancer-related pain can be controlled using guidelines established by the World Health Organization (WHO)[1]. Even when the basic principles of analgesic drug use are adhered to, some patients experience inadequate pain relief or considerable adverse effects from systemic opioids, and the 10% of patients with unrelieved cancer pain may still represent a significant number[2]. Some of these patients experience severe pain due to a failure to achieve adequate analgesia despite sequential escalation of the dosage of strong opioids, or the development of side effects, such as nausea, vomiting, constipation, drowsiness, and sedation, which limit further dose escalation[3].

Switching opioids or changing the route of opioid administration may improve patient response in most cases, and only a small proportion of patients with cancer pain should be considered candidates for spinal administration[4]. Spinal opioids are indicated if systemic therapy has failed, either because of inadequate analgesia or because of intolerable side effects[5].

The use of patient-controlled epidural analgesia in the acute, postoperative, and obstetric populations has been well described. However, there have been only a few reports of the use of patient-controlled intrathecal analgesia for cancer pain[6].

We report on an outpatient with severe cancer pain that was successfully managed with long-term intrathecal infusion of morphine, bupivacaine, and

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Table 1 Laboratory data

WBC	13,000 × 10^3 /m^3
RBC	342 × 10^3 /m^3
Hb	10.7 g/dL
Ht	34.4 %
PLT	31.7 × 10^3 /m^3
AST	19 IU/L
ALP	17 IU/L
LDH	169 IU/L
ALP	380 IU/L
T-Bil	0.4 mg/dL
TP	6.9 g/dL
Alb	3.5 g/dL
BUN	14 mg/dL
Cr	0.62 mg/dL
CA 19-9	below 1.2 U/mL
CEA	1.6 ng/mll
CRP	9.55 mg/dL

racemic ketamine via a patient-controlled delivery system. The pain intensity was measured with a numerical rating scale (NRS) score.

Case Report

The patient was a 49-year-old woman with a history of gastric adenocarcinoma. She had undergone total gastrectomy and splenectomy 4 years before presentation. She had undergone percutaneous nephrostomy to treat bilateral hydronephrosis caused by cancer invasion of the ureter. Local retroperitoneal invasion of the cancer had caused severe back and upper abdominal pain. There was no evidence of metastasis to the liver, lung, or bone on computed tomography, positron emission tomography, or radioisotope imaging. No obvious carcinomatous peritonitis was found. **Table 1** shows the laboratory data. The performance status (PS) was 2.

Medications used for pain management included oxycodone (80 mg/day) and loxoprofen (180 mg/day).

The patient continued to experience a dull ache throughout the waist and back despite oxycodone rescue medication. She rated the pain at 9 on the NRS and had increasing nausea and vomiting despite treatment with prochlorperazine and metoclopramide, for which she was referred to the Department of Anesthesiology.

Oxycodone was replaced by transdermal fentanyl (50 μg/hr), and periodic lumbar epidural block was performed. The pain was subsequently rated as 4 on the NRS. We added chlorpheniramine maleate to manage the nausea, and the patient's appetite began to improve. She was subsequently discharged from our institution. However, 1 month later, she began to vomit frequently and had difficulty taking rescue oxycodone orally; therefore, she was readmitted to our hospital. Although morphine administration at 40 mg/day through intravenous patient-controlled analgesia (PCA) was started, she rated the pain as 4 on the NRS, and rescue medication was frequently administered. Therefore, the dosage of morphine was slowly increased to 100 mg/day. She rated the pain as 3 on the NRS but began to feel sleepy and continued to have nausea.

Because this patient had a life expectancy of at least 6 months, we decided to implant an intrathecal catheter. As a blocking test, 2 mL of 0.05% bupivacaine and 1 mg of morphine were administered in a single intrathecal injection. She rated the pain as 0 on the NRS, and the effect lasted for 12 hours. Subsequently, we inserted a catheter into the intrathecal space in the lumbar column (L2-L3, paramedian approach) and implanted a port in the wall of the upper abdomen. The catheter tip was placed at the level of the 10^{th} thoracic vertebra. Continuous spinal administration of morphine (1 mg/day) with 0.05% bupivacaine via a pump was started at a rate of 0.5 mL per hour. Until an appropriate dose of intrathecal morphine was determined, intravenous PCA was co-administered. Ten days later, the morphine dose was stabilized at 12.5 mg/day, and the intravenous PCA was discontinued. Intrathecal morphine PCA was used instead, and the patient was discharged 16 days after implantation.

We asked a local clinician to change the port needle and sterilize the catheter insertion site, and the patient agreed to visit our outpatient clinic every week. It became possible for her to enjoy everyday life as before, including bathing twice a week, housekeeping, and shopping. The PS improved from 2 to 1. She reported good pain control within 15 minutes after pushing the PCA button for the intrathecal morphine. Taking the

Table 2 Drug requirements for intrathecal, intravenous, transdermal and oral administration

Time after intrathecal therapy	Day 0	Day 1	Day 5	Day 10	Day 16	Day 76	Day 96	Day 124
Intrathecal								
Morphine (mg/day)		1	5	12.5	15	30	30	45
Bupivacaine (%)		0.05	0.05	0.05	0.05	0.125	0.125	0.125
Ketamine (mg/day)							15	20
Intravenous								
Morphine (mg/day)	100	50	50					
Transdermal								
Fentanyl (μg/hr)						50	50	75
Oral								
Loxoprofen (mg/day)			180	180	180			
Meloxicam (mg/day)						10	10	10

number of rescue medication doses and other factors into consideration, 76 days after implantation we increased the dosage of intrathecal morphine and bupivacaine to 30 mg/day and 0.125%, respectively. Transdermal fentanyl was added to treat the nausea due to the increased morphine dosage. Ninety-six days after implantation, the dosage of transdermal fentanyl was 50 μg/hr, and the patient rated the pain as 6 on the NRS. An additional 15 mg/day of intrathecal ketamine decreased the pain to 3 on the NRS. Later, fascial pain developed in the upper part of the back, which we managed with a periodic thoracic epidural block. She was able to spend most of her time at home, although she was hospitalized for a short period. At 124 days following implantation, the pain-control medications included 45 mg/day of intrathecal morphine, 20 mg/day of intrathecal ketamine and 75 μg/hr of transdermal fentanyl (**Table 2**). She was transferred from our hospital to a neighboring hospital, where she received intrathecal analgesia and passed away 4 months later.

Discussion

We used intrathecal infusion of morphine, bupivacaine, and racemic ketamine via PCA to successfully manage cancer pain in a patient who had had severe side effects due to systemic morphine adminstration. Intrathecal administration reduced nausea, vomiting, and somnolence and facilitated early hospital discharge. In addition, a patient-controlled delivery system simplified opioid administration and gave the patient the freedom to control symptoms associated with increased activity. The PS improved when the route of opioid administration was changed. At the outpatient clinic we titrated the dosages of intrathecal bupivacaine and ketamine according to the patient's pain, and there were no signs of motor paralysis, psychomimetic alteration, or neurological dysfunction. She maintained some independence and was able to walk to our outpatient clinic. There were no symptoms of infection related to the intrathecal route.

Opioids remain the mainstay for pain control in cancer patients. Opioids are usually started via the oral or parenteral route, and the dosage is increased until side effects prevent further increases or until the pain is adequately controlled. If pain persists, the options include neuraxial opioids[7]. Depending on the life expectancy of the patient, opioids can be delivered epidurally via an external pump or intrathecally via an implanted pump. Even when effective, prolonged epidural administration can result in frequent technical complications, such as obstruction by epidural fibrosis and dislocation of catheters[8]. Because the life expectancy of our patient was at least 6 months, we decided to implant an intrathecal catheter.

The dosage should be adjusted by age, injection site, and the patient's condition and degree of tolerance to opioids[9]. An oral: intrathecal ratio of 200 : 1 to 300 : 1 has been suggested, and some

predictive factors, including previous opioid dosage, have been recommended[10]. We consider the morphine oral: intravenous: intrathecal ratio to be 300 : 100 : 1. We started intrathecal morphine at a dose of 1 mg/day. However, 10 days were needed to titrate the intrathecal morphine. Long-term dosage titration could be detrimental for patients, because it increases their suffering and reduces their compliance. Recently, Mercadante *et al.* suggested that the intrathecal treatment be started with an oral: intrathecal morphine conversion ratio of 100 : 1, and local anesthetics at the most convenient clinical doses provided a rapid and long-term improvement of analgesia, with reduced adverse effects and opioid consumption[2].

Co-administration of drugs with different mechanisms of action, such as an opioid and a local anesthetic, may yield additive or supra-additive effects and provide good analgesia while decreasing adverse drug effects. Such potentiation can be useful in decreasing the dosage and the specific side effects produced by either drug alone[11].

In the present case, because intrathecal catheter was managed at home for a long time, we paid close attention to infection. We asked a local clinician to change the port needle and sterilize the catheter insertion site twice a week. We educated her family and asked them to remove the port needle, which prevented infection related to the intrathecal route throughout treatment. Intrathecal drug delivery without complications is possible at home if healthcare professionals take precautions in refilling the syringe driver and connecting the system, and if they maintain continuous communication between the family and the team, make frequent visits, and teach the family about the system. Most family members preferred not to handle the system directly[11]. Careful follow-up at home by an experienced healthcare professional prevents complications due to spinal catheterization in the home-care setting.

Our patient showed that co-administration of racemic ketamine may be effective for treating chronic malignant pain and providing good pain relief without causing undesirable side effects. Intrathecal ketamine was described 20 years ago[12], but there have been only a few reports on its continuous intrathecal administration. An advantage of the intrathecal route is a lower required drug dosage, which can reduce side effects. In our patient, a daily dose of 20 mg was sufficient to control the pain. There were no signs of opioid withdrawal or side effects, such as arterial hypertension, psychomimetic alterations, and neurological dysfunction. The mechanism of action of ketamine may be the direct antinociception elicited by inhibition of spinal N-methyl-D-aspartate (NMDA) receptors, or the reduction in morphine tolerance, thereby increasing morphine antinociception at the spinal level[13]. This mechanism was confirmed by a recent study in which neuraxial co-administration of ketamine and morphine increased both visceral and somatic antinociception[14]. Racemic ketamine, a noncompetitive NMDA receptor antagonist, as well as its active enantiomer S (+)-ketamine, has been advocated for intrathecal and epidural use in the management of severe intractable pain unresponsive to opioid escalation[15]. Although racemic ketamine is a half-mixture of S (+)-ketamine and R (−)-ketamine, only racemic ketamine is available in Japan. Regarding the potential neurotoxicities of ketamine for neuraxial use, histopathological changes of the spinal cord have been reported following long-term intrathecal administration of ketamine[16]. In our patient, we did not observe any neurological deficit attributable to possible intrathecal racemic ketamine toxicities. The safety of combining ketamine, morphine, bupivacaine has not been addressed by preclinical studies. This route of administration should be considered as a last resort, because of the potential for neurotoxicity.

We recommend the following indications for cancer pain management with intrathecal PCA: the total opioid dosage administered is equivalent to 300 mg/day oral morphine; previous trial of at least 3 different opioids, including multiple switching failures and 2 routes of administration, including one intravenous trial; intolerance of side effects; and no concurrent hemostatic dysfunction[2]. We advocate the use of ketamine in the management of severe intractable pain unresponsive to intrathecal opioid escalation of more than 30 mg/day.

In conclusion, patient-controlled intrathecal infusion of morphine, bupivacaine, and racemic ketamine improved symptom control in a patient with intractable cancer pain.

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