

Case Report

e Complications after Intrathecal Drug Delivery Due to the Underlying Malignancy in Two Patients with Intractable Cancer Pain

Thomas Chai, MD, Brian M. Bruel, MD, Kent H. Nouri, MD, and Larry C. Driver, MD

From:
University of Texas, M.D.
Anderson Cancer Center,
Houston, TX

Address Correspondence:
Thomas Chai, MD
MD Anderson Cancer Center
University of Texas
Houston, TX
E-mail: tchaimd@gmail.com

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Intrathecal drug delivery is a mode of analgesic delivery that can be considered in those experiencing both refractory pain and excessive side effects from opioid and adjuvant analgesic use. Delivery of analgesic agents directly to the cerebral spinal fluid allows binding of the drug to receptors at the spinal level. Therefore, a reduced analgesic dosage can be afforded, resulting in reduction of drug side effects due to decreased systemic absorption. Drug delivery into the intrathecal space provides this benefit, yet it does not eliminate the possibility of drug side effects or risks of complications.

Complications from this route of administration may be seen in the perioperative period or beyond, including infection, inflammatory mass, bleeding, and catheter or pump dysfunction, among others. This may manifest as new/worsening pain or as a neurologic deficit, such as a sensorimotor change and bladder/bowel dysfunction. Urgent evaluation with a detailed physical examination, device interrogation, and other workup including imaging is called for if symptoms suspicious for device-related problems arise. For the cancer pain patient, the underlying malignancy should also be considered as a potential cause for these new symptoms after intrathecal system implantation.

We present 2 such cases of complications in the cancer pain patient after intrathecal drug delivery due to progression of the underlying malignant process rather than to surgical or device-related problems. The first patient had a history of metastatic osteosarcoma who, shortly after undergoing an intrathecal drug delivery trial with external pump, presented with new symptoms of both pain and neurologic changes. The second patient with a history of chondrosarcoma developed new symptoms of pain and sensorimotor change several days after intrathecal drug delivery system implantation.

Key words: Intrathecal analgesia, intrathecal drug delivery, perioperative complications, cancer pain, malignant pain, pain pump

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Intrathecal drug delivery is an established option for the management of cancer pain (1-3), particularly in those experiencing significant adverse effects from escalating doses of opioid analgesics and non-opioid adjuvants. Administration of opioids directly to the central nervous system results in analgesia using much lower dosages with fewer adverse effects compared to systemic administration (1-3). There are, however, a number of potentially serious complications associated with this mode of drug delivery. Patients may exhibit

signs or symptoms that suggest an underlying problem with the intrathecal drug delivery system due to a number of causes, such as infection, hematoma, hardware failure, or catheter-related problems, among others (1-5). In addition to these causes, in the cancer pain patient, the underlying malignancy must also be considered as the cause of new symptoms developing perioperatively after intrathecal drug delivery. We present 2 such patients who experienced the onset of new pain and neurologic symptoms shortly after

intrathecal drug delivery due to the progression of the underlying malignant process.

CASE REPORTS

Case 1

A 28-year-old woman with an approximately one-year history of high-grade sarcoma of the right upper extremity (status post resection and chemotherapy), with known liver, lung, and bone metastases came to our clinic for evaluation and management of nociceptive and neuropathic pain in the involved areas. She was initially placed on an oral analgesic regimen that was eventually adjusted to include scheduled methadone and for breakthrough pain, both hydromorphone and fentanyl transmucosal lozenges, along with adjuvant medications. There appeared, however, to be continued suboptimal control of her pain. It was thought that she would benefit from intrathecal analgesic delivery and the patient subsequently underwent an intrathecal trial with external pump (Curlin 6000 CMS™ Ambulatory Infusion System, Curlin Medical, Huntington Beach, CA),

delivering hydromorphone (0.1 mg/mL) and bupivacaine (0.1 mg/mL), both infusing at 0.5 mL/hr (1.2 mg/day).

Two days later, she noted fever and increasing back and left hip pain, which prompted her to visit the emergency room. Fever work-up in the emergency room was negative and the patient was subsequently discharged home. She then presented to our clinic the next day and the catheter was removed due to a noted malfunction (catheter disconnect), but the trial was considered a success in that the patient reported significant reduction in overall pain severity during the trial. The following day, the patient noted progressive difficulty in ambulating due to lower extremity weakness and decreased sensation. She returned to the emergency room and on examination was noted to have decreased sensation to light touch in all key lower limb dermatomes, brisk reflexes in the lower limbs, and 3/5 or less strength in all key lower limb myotomes. She also demonstrated clonus in the right foot and a Babinski response in the left foot. Magnetic resonance imaging (MRI) of the thoracic and lumbar spine revealed extensive osseous metastatic disease in the thoracolumbosacral spine and iliac bone, with new epidural extension at multiple levels, causing spinal canal narrowing at T3-T8, L5, and S1 (Fig. 1). The patient was therefore diagnosed with thoracic spinal cord compression, but she was deemed not be a neurosurgical candidate due to the complex nature of her spinal metastases, as well as other significant comorbidities. The patient received steroid therapy and palliative radiation therapy to the spine instead. Once stable, she eventually underwent intrathecal pain pump implantation, infusing hydromorphone (10 mg/mL) and bupivacaine (10 mg/mL), at 1.999 mg/day. She was discharged to hospice shortly afterwards.



Fig. 1. Sagittal MRI view of the thoracic spine (T2-weighted). Epidural disease is seen displacing the cord and infiltrating the neural foramina at multiple thoracic vertebral levels, including at T8 (labeled).

Case 2

A 45-year-old woman with an approximately one-year history of chondrosarcoma of the right chest wall, status post chemotherapy and laparoscopic thoracotomy, right middle lobe wedge resection, and right T7-T9 rib resection, was seen by our service for persistent right chest wall pain of a mixed-nociceptive type. She had been on escalating doses of scheduled extended-release oxycodone, breakthrough hydromorphone, and gabapentin, with still inadequate pain control. It was thought that her pain would be better controlled with intrathecal drug delivery. Therefore, 2 weeks after initial evaluation, she underwent an intrathecal trial with ziconotide (0.25 mcg/mL) and bupivacaine (0.25 mg/mL) with external pump, infusing at 0.2 mL/hr (1.2

mcg/day and 1.2 mg/day, respectively), reporting good pain relief. She subsequently underwent a permanent intrathecal drug delivery system implantation (Synchromed® II drug pump, Medtronic, Minneapolis, MN) 2 weeks later, delivering ziconotide (10 mcg/mL) and bupivacaine (10 mg/mL) at 2.5 mcg/day and 2.5 mg/day, respectively.

A few days after the procedure, the patient experienced a new burning-quality pain in the bilateral lower abdomen, hip, and pelvic region. Her symptoms progressed over the following several days to include urinary retention and distal lower limb paresthesias. She presented to the emergency room, where physical examination revealed no focal motor or sensory deficits in the lower limbs, except paresthesias elicited to light touch in the soles of her feet. A Foley catheter was placed for urinary retention. Telemetric interrogation (N'Vision® Clinician Programmer, Medtronic, Minneapolis, MN) of the pain pump was unremarkable. MRI of the thoracolumbar spine showed metastatic chondrosarcoma with new involvement of the right paraspinal region, centered at the T10/T11 intervertebral disc space, with extension epidurally from T9-T12, compressing and displacing the thoracic cord at these levels (Fig. 2). Ultimately the patient received chemotherapy and underwent extensive back and chest wall surgery for tumor resection. The patient did not require pump/catheter revision or explantation and continues to be followed by our service for oral and intrathecal analgesic medication adjustment.

Discussion

Intrathecal drug therapy is an alternative method in managing refractory pain from various conditions, including those related to cancer pain. This mode of drug delivery provides a number of advantages. For instance, in a recent audit in a tertiary care institution by Pasutharnchat and colleagues (6), 29 cancer pain patients (most with metastatic disease) who underwent intrathecal catheter implantation for drug delivery had a significant decrease in pain intensity (70% reduction) and a reduction in side effects from opioids. In addition, the complication rate from the treatment was minimal. A prospective longitudinal study by Smith and Coyne (2-3) describes patients with refractory cancer pain deriving similar significant benefits from intrathecal drug delivery systems despite having comprehensive medical management.

Delivering analgesic medication to spinal receptors via the cerebral spinal fluid (CSF) may explain the im-



Fig. 2. Axial (horizontal) MRI view of the thoracic spine (T2-weighted). Right epidural tumor (asterisk) at T10 vertebral level compressing and displacing the cord towards the left.

proved efficacy, tolerability, and functional outcomes compared to standard analgesic regimens administered systemically, since intrathecal doses are 1/100th to 1/200th of the morphine-equivalent daily systemic dose (7). The US Food and Drug Administration has approved both preservative-free morphine sulfate and ziconotide for intrathecal use; however, there are a number of other analgesics that have been used successfully, such as hydromorphone, fentanyl, clonidine, sufentanil, local anesthetics, or a combination of the above (8). As such, the 2007 Polyanalgesic Consensus Conference includes hydromorphone as first-line therapy for intrathecal use.

There are a number of considerations for selecting appropriate candidates for intrathecal drug therapy. An appropriate candidate would meet the following general criteria (7) — pain refractory to conservative therapy; pain with an identifiable organic cause; no significant psychological dysfunction; no further treatment for the underlying cause of the pain is appropriate or possible; patent spinal canal; life expectancy more than 3 months; patient had a successful trial with either epidural or intrathecal analgesia (single injection, multiple injection, or temporary catheter with continuous infusion); and no contraindications to surgery (such as active infection or coagulopathy). The physician therefore must obtain a thorough pain assessment history, functional assessment, psychologi-

cal evaluation, and medical and radiographic studies in the work-up (7). In addition, Yennurajalingam et al (9) suggest that a well-conceived personalized therapy program for each patient should be attempted to maximize medical management prior to consideration of intrathecal drug delivery.

After implantation of the intrathecal drug delivery system, there should be close follow-up perioperatively to assess for potential complications. Hemorrhage leading to spinal hematoma can cause neurologic injury, which may manifest as sudden increase in back pain, progressive weakness or numbness in the lower limbs, or changes in bladder/bowel function. This would require urgent neurosurgical intervention for decompression. Wound infection may involve the pump pocket, the lumbar wound, or abscess and meningitis. This is usually treated with antibiotics, but may require surgical debridement and explantation of the drug delivery system. CSF leakage may lead to spinal headache or hygroma, which is usually managed with an epidural blood patch or by purse-string suturing of the dura surrounding the catheter (10). Catheter-related complications include dislodgement/migration from the intrathecal space, fracture/breakage, kink/occlusion, puncture/cut, in order of decreasing frequency (4-5). Ko and Ferrante (11) report a case of catheter migration into the intervertebral foramen in one patient, manifesting as new-onset lumboradicular pain in an L4 nerve root distribution. Catheter evaluation may include a catheter dye study using fluoroscopy. Catheter revision surgery would be required for these complications. Inflammatory masses at the catheter tip may cause symptoms usually weeks to months after implantation. An example is a case report from Shields et al (12) that describes a patient with cauda equina syndrome due to catheter tip granuloma formation compressing the conus medullaris. A rare event of catheter insertion into the cord has also been reported (13), with neurologic injury manifested by motor weakness and loss of pain/temperature resulting from a traumatic syrinx. There may be problems with the infusate or its programming. Ruan et al (14)

report a patient who suffered respiratory depression after delayed refill of the intrathecal pump, suggesting that there was a loss of opioid tolerance in the interim prior to pump refill.

New symptoms after intrathecal drug delivery may, however, be associated with the underlying condition in the cancer pain patient, rather than from the aforementioned complications. Appelgreen et al (15) recognized that epidural metastases were associated with refractory cancer pain after intrathecal drug delivery. In their study the presence of epidural metastases affected catheter insertion, daily analgesic dosage, and complications of the hardware only when spinal canal stenosis was also present. There was also a higher occurrence of paraplegia due to injury during attempted dural puncture secondary to a reduction in the posterior subarachnoid space from epidural tumor compression. The authors explain that neurological deterioration after intrathecal catheterization in the observed patients was best explained by a number of mechanisms: (a) unknown epidural tumor at the site of dural puncture may have been injured, resulting in edema/bleeding and cord/nerve compression and (b) loss of CSF below the level of subarachnoid block (from tumor mass effect) after dural puncture causes "spinal coning," which is impaction of a spinal cord tumor after removal of CSF, as the CSF may have acted as a buffer between the cord and the extramedullary tumor. Yet another proposed mechanism is epidural venous engorgement from reduced intrathecal pressure after reduction of CSF pressure. In our 2 cases, however, the evidence suggests that a progression of disease likely explained the new onset of symptoms.

CONCLUSION

Careful patient selection and meticulous surgical implantation may reduce perioperative complications and post-implantation adverse outcomes. In addition to routine evaluation of the intrathecal drug delivery system, work-up for new symptoms after intrathecal drug delivery in the cancer pain patient should include diagnostic imaging to exclude progression of the underlying malignancy.

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