Ketamine Analgesia for the Opioid-Tolerant Cancer Patient

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CASE STUDY

The Inpatient Pain Medicine team at The Johns Hopkins University, Baltimore, MD, USA was consulted to assist in the care of a 32-year-old woman with metastatic cervical cancer. She had been diagnosed with cervical cancer in 1997 and subsequently had a radical abdominal hysterectomy and salpingo-oophorectomy, followed by chemotherapy and radiation therapy. In 2001, her disease recurred with multiple complications, leading to multiple procedures, including:

- multiple abdominal surgeries for bowel obstructions
- bowel diversion with ileostomy
- cholelithiasis
- endoscopic retrograde cholangiopancreatography (ERCP)
- pancreatic duct stenting, bilateral ureteral diversion
- nephrostomy
- deep venous thrombosis (DVT)
- Greenfield filter (Boston Scientific, Natick, MA, USA) placement.

When the Pain team initially saw the patient, she complained of severe abdominal and pelvic pain, despite strong opioid therapy consisting of morphine by intravenous patient-controlled analgesia (IV-PCA), delivering a continuous infusion of 30 mg/h, and 6-mg boluses, with a lock-out of 6 min. Interestingly, she had recently experienced epidural analgesia after an exploratory laparotomy. She had found epidural analgesia superior to IV-PCA, and was therefore very receptive to a trial of intrathecal analgesia. The intrathecal catheter was placed and a trial begun with intrathecal morphine. We quickly decided to add bupivacaine. The intrathecal trial was a success, reducing her visual analog scale (VAS) pain score from 5–6 (out of 10) to 2, on 8 mg/day of morphine and 4 mg/day of bupivacaine. There was a 2-week delay until implantation of a permanent infusion system because the patient developed hyponatremia and a DVT that had to be managed. The smallest possible pump was chosen for implant (a constant-flow pump with 16-cc pump volume and 0.5 cc/day flow rate [Arrow International, Inc., Reading, PA, USA]) because the patient was extremely cachectic. After pump implantation the patient was on an IV-PCA of morphine, at a dose of 3-mg/h continuous infusion, 3-mg demand, and 6-min lock-out.

She was discharged from the hospital with excellent pain control and was even able to travel on vacation with her family. Unfortunately, her cancer progressed, and 4 months later eroded into her hip joint, causing a pathologic hip fracture and severe pain. Orthopedic surgery offered the patient a partial pelvic replacement, which she accepted. At this time, her pain medication had greatly increased to an intrathecal infusion of morphine (10 mg/day), bupivacaine (6 mg/day), and an IV-PCA of hydromorphone, delivering a continuous infusion of 14 mg/h, with 8-mg bolus and 10-min lockout. She had myoclonus from the high doses of opioid. We treated her myoclonus effectively with oral clonazepam and increased her IV hydromorphone, without apparent analgesia. Her intrathecal therapy was also increased to 15 mg/day of morphine and 12 mg/day of bupivacaine, with only minimal effect. At this point she was taken to the operating room for the partial pelvis replacement.

We discussed the patient's anesthetic plan with the attending anesthesiologist and jointly decided to use ketamine as an IV anesthetic. We chose ketamine because of the high doses of parenteral and intrathecal

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opioids that the patient was getting. Both the pain team and the anesthesiologist felt that we could not provide analgesia with more opioids. The anesthesiologist was also reluctant to use spinal anesthesia with local anesthetic because of the resulting sympathectomy and the planned procedure. Partial pelvis replacement has the potential for massive intraoperative blood loss and sympathectomy makes resuscitation during this loss more difficult. Post-operatively, ketamine boluses (0.25–0.5 mg/kg IV) were used for pain control in the intensive care unit (ICU). These boluses completely relieved the patient's pain, whereas high-dose hydromorphone did not provide any analgesia. While in the ICU, she was also given scheduled ketamine by IV bolus (0.5 mg/kg every 8 h), which reduced her numerical rating scale (NRS) pain scores by about 30%.

The partial pelvis replacement was not performed secondary to an infected hip joint found at operation; instead, the femoral head was resected, with a planned pelvis replacement 6 months later. Over the following week, the patient's intrathecal bupivacaine was increased and her pain control improved, most likely because of both the hip surgery and the increased intrathecal therapy. She was discharged from hospital 8 days after surgery.

We did not give this patient ketamine after discharge because her pain was under control with the combination of intrathecal morphine/bupivacaine and IV-PCA hydromorphone. If her pain had not been controlled we could have given her ketamine at home orally or by nasal spray, 0.25-0.5 mg/kg three-times-daily. In fact we do have a patient with chronic benign pain that is using a ketamine nasal spray. Unfortunately, this patient's disease was relentless. Nine weeks later she developed another deep venous clot, which progressed into a pulmonary embolus despite Greenfield filter placement and anticoagulation. It had been 25 weeks since her intrathecal pump implant. Her mental status had deteriorated significantly and assessing her level of pain was difficult. She died 1 week later from her pulmonary embolus and multisystem organ failure.

Discussion

The World Health Organization's analgesic ladder uses opioid medications as a mainstay of cancer pain management. Unfortunately, in some patients, including this one, the pain is opioid resistant [1–3]. Special strategies are needed for these patients, which may include agents to improve opioid sensitivity, adjuvant analgesics, and neural blockade techniques.

Opioid effectiveness may be improved by drugs that either directly or indirectly increase the analgesia produced by a unit dose of opioid, or by drugs that reduce opioid side-effects and thus allow a larger dose of opioid to be used. Drugs that block the *N*-methyl-D-aspartate [NMDA] receptor, a specific glutamate receptor subtype, may reduce opioid tolerance [4,5]. Ketamine is the prototypical NMDA antagonist in use today, while methadone and dextromethorphan also have NMDA antagonist properties [6,7]. Ketamine is classified as a dissociative IV anesthetic agent [8], but is also a direct analgesic [9].

Ketamine has been used for the management of both cancer pain and chronic pain in many studies and case reports (Table 1) [5,10–16]. Lauretti et al. gave oral ketamine (0.5 mg/kg twice daily) to patients with cancer pain that was not relieved by 80–90 mg/day of oral morphine [17]. Their study was a randomized, controlled trial in patients with VAS pain scores of approximately 7.6. All patients were allowed to adjust their morphine use as needed during the trial. After 30 days, the control and ketamine groups had similar VAS scores, but the ketamine group was using significantly less morphine. Jackson et al. performed an open-label study of 'burst ketamine' given by continuous subcutaneous infusion for refractory cancer pain [18]. Thirty-nine patients with a variety of diagnoses were enrolled, but all were on high doses of opioid (mean dose 231 mg/day of parenteral morphine or its equivalent). Patients with somatic pain responded to ketamine with dramatically decreased NRS scores in 15 of 17 cases, while those with neuropathic pain improved in 14 of 23 cases. Ketamine was given in escalating doses over 3–5 days, with many of the patients requiring the highest dose allowed (500 mg/day). Mercadante et al. performed a randomized, blinded, controlled study of IV bolus ketamine in 10 patients with cancer pain that had not responded to morphine (30–300 mg in parenteral equivalent doses) [19]. Ketamine, but not saline, dramatically improved pain scores at doses of 0.25 mg/kg and 0.5 mg/kg. The analgesia lasted 3 h in all cases, and up to 12 h in one subject.

In addition to the clinical data, there is good experimental evidence to support the use of ketamine when opioids are ineffective. High-dose opioids can induce delayed hyperalgesia in a rat model of pain [20]. Ketamine pretreatment prevents the development of this hyperalgesia [20]. Thus, ketamine may have two actions, a direct analgesic effect [7–9], and a reversal of opioid hyperalgesia/desensitization.

Ketamine is a valuable tool for cancer pain relief, but is associated with significant drawbacks, and should be used cautiously. As an IV anesthetic agent, ketamine will

Table 1. Studies of ketamine analgesia.

Author [reference]	Pain mechanism	Number of subjects	Efficacy	Dose	Route	CNS adverse effects**
Backonja et al. [10]	Chronic neuropathic	6	5/6	0.25 mg/kg single bolus	IV 5/6	NA
Enarson et al. [12]	Chronic neuropathic	21	11/21	220 mg/day	PO	9/21
Jackson et al. [18]	CA-somatic	17	15/17	100–500 mg/day	IV	12/41
	CA-neuropathic	23	14/23	100–500 mg/day	IV	12/41
Kannan et al. [14]	CA-neuropathic	9	7/9	0.5 mg/kg TID	PO	6/9
Lauretti et al. [17]	CA-NOS	15	*	0.5 mg/kg BID	PO	6/9
Mercadante et al. [19]	CA-NOS	10	*	0.25 mg/kg single bolus	IV	3/10
	CA-NOS	10	*	0.5 mg/kg single bolus	IV	1/10
Oshima et al. [16]	CA-NOS	18	13/18	2.5–15 mg/h	CSQI	2/15

*Efficacy shown by overall decrease in opioid use in treated group.

**Defined as sedation, drowsiness, hallucinations, and dissociative sensations.

BID: two doses per day; CA: cancer pain; CNS: central nervous system; CSQI: continuous subcutaneous infusion; IV: intravenous dosing; NA: not available; NOS: not otherwise specified; PO: oral dosing; TID: three doses per day.

depress mental status, and even induce general anesthesia if used at higher doses (1–2 mg/kg IV bolus) [8]. Ketamine is a sympathetic stimulant and can produce tachycardia, hypertension, excessive salivation, and elevated intracranial pressure [8]. At the lower doses used in analgesic studies, the main side effects of ketamine are hallucinations, intoxication ('feeling drunk'), and drowsiness. Hallucinations are a dose-dependent effect, seen in four of 10 patients given 0.5 mg/kg by slow bolus (over 30 min) in one study [19], but only three of 39 in another [18]. Sedation, 'spaced out' feelings, and dizziness, were reported in nine of 39 patients in one study [18]; all patients improved when the ketamine dose was reduced. Patients given ketamine by constant infusion had seemingly fewer side effects than patients given intermittent boluses (Table 1), despite the fact that the patients on infusions received a higher total dose. Even though none of the more serious side effects were noted when ketamine was used at low doses, appropriate care should be taken when initiating ketamine therapy. Any IV bolus dosing of ketamine should be done with hemodynamic monitoring and airway and resuscitation equipment immediately available. During the initial phases of subcutaneous or oral dosing, there should be frequent mental status and hemodynamic checks (at least daily).

We used ketamine for analgesia in the acute period in which opioids were ineffective. The above discussion shows that ketamine may also be used chronically for analgesia. Other techniques to improve long-term analgesia include opioid rotation, and the use of adjuvant agents, such as clonidine, tricyclic antidepressants, and non-steroidal anti-inflammatory drugs [3]. Interventional techniques for cancer pain control should also be considered for opioid-resistant cancer pain. Intrathecal or epidural delivery of local anesthetics, with or without opioids, and neurolytic techniques, such as celiac plexus block, superior hypogastric plexus block, and spinal neurolysis, can provide dramatic benefit for the appropriate patient. Ketamine should be in the armamentarium of pain specialists and considered along with other adjunctive and interventional techniques.

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