Ketamine for Pediatric Cancer Pain: A Flip of a Coin?  
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Case 1
Patient A is an 18 year old female with past medical history significant for remission from T-cell lymphoblastic lymphoma and a new diagnosis of acute myeloid leukemia one year after matched sibling stem cell transplant for treatment related myelodysplastic syndrome. She was admitted following her diagnosis of AML for chemotherapy. She had a prolonged hospital course that was complicated by paraneoplastic disorder and severe multisystem autoimmune disorder. The patient required multiple admissions to the pediatric intensive care unit where she was treated for septic shock. During the first 2 months of her hospital admission, she had intermittent pain including general myalgias, headaches, and post-procedural pain. These pain complaints were well controlled with PRN doses of hydromorphone and oxycodone, although she occasionally needed a hydromorphone patient controlled analgesia (PCA) for a few days at a time.

She then started having increase pain due to onset of sternocleidomastoid myositis which resulted in dysphagia and pain with neck movement. She was started on a fentanyl PCA that was increased from basal dose of 7mcg/hr with PCA bolus of 25mcg q10min to a basal dose of 350mcg/hr with PCA bolus of 70mcg q10min over 3 weeks. Her condition worsened with a new pulmonary inflammatory concerning for fungal infection. She became sedated and hypoxic with increased work of breathing. During this time the patient made the decision with her family to be DNR/DNI.

The pediatric chronic pain service was consulted to help with pain control and possibly comfort care. A ketamine infusion was started at 0.1mg/kg/hr. Her pain decreased within a week to 150mcg/hr basal rate with PCA bolus of 125mcg q10min which she used an average of 1-3 times per hour. Her level of consciousness and work of breathing improved significantly over the course of a few days. Ketamine infusion was titrated up slowly over the following month to 0.28mg/kg/hr. Patient was more comfortable and alert and able to participate in physical therapy. Oxygen requirements of HFNC decreased to room air within 3 weeks. She received more chemotherapy as palliative treatment for refractory AML. During the 16 days before anticipated discharge, ketamine was titrated to off which patient tolerated well. She was discharged on Fentanyl PCA with palliative care.

Case 2
Patient B is a 13 year old female with a history of disseminated metastatic osteosarcoma and progressive left retro-orbital tumor. The retro-orbital tumor was surgically debulked in April 2015 followed by chemotherapy. Patient had stabbing facial pain in the distribution of V1, V2, and V3 that developed a few weeks after surgery and was initially tolerable with Fentanyl transdermal patch at 75mcg/hr. Her pain worsened over a few weeks and oxycodone 40mg BID was started. Within days, pain continued to escalate and oxycodone was increased to 40mg q4hrs. Other components of her analgesic regimen included lorazepam and pregabalin. When pain became increasingly severe, she was admitted to the hospital for pain management.

The pediatric chronic pain team was consulted by the primary service and recommended a ketamine infusion which was started at 0.1mg/kg/hr. It was quickly increased to 0.2mg/kg/hr during the first day due to escalating pain. A part of the multimodal regimen, she continued her home medications of pregabalin, clonidine, sertraline, and received fentanyl PCA as well as RN bolus dosing. The patient failed to get much relief from the current pain regimen, the pediatric chronic pain attending performed a gasserian ganglion block using 0.25% Bupivacaine. The block provided partial relief for approximately 24 hours but pain returned to baseline within 2 days. During this time, alternatives for pain management were discussed with the patient and family. It was decided to start a ketamine infusion. The patient tolerated the procedure well and received fentanyl PCA as well as RN bolus dosing. She continued to experience facial pain that was 8-10 out of 10 on a numeric pain scale. Ketamine infusion was increased from 0.2mg/kg/hr to 0.5mg/kg/hr over the next 6 days. This increase did not abate her pain.

Neurosurgery performed a palliative debulking of the osteosarcoma that was complicated by a postoperative epidural hematoma. The patient did not experience relief of pain with this procedure, and the patient subsequently underwent radiation of the area. Ketamine was further increased to 0.6mg/kg/hr, methadone and oxycodone were added but had little benefit initially. The team started clonidine and sertraline in the following weeks. Over the course of the radiation treatment, her pain began to ease. She had very few side effects from the ketamine which included brief hallucinations for a few days only. She was eventually discharged on ketamine infusion with methadone, fentanyl PCA (no basal), pregabalin, lorazepam, clonidine, sertraline, and oxycodone.

Discussion
Ketamine is an NMDA antagonist that has been used as an adjunct for treating cancer pain and other complex/chronic pain syndromes in recent years. Cancer patients may have pain as a result of neuropathic pain and increase opioid requirements. Ketamine is successfully used in some cancer patients to treat moderate to severe neuropathic pain and decrease opioid requirements. Our two patients had dramatically different results from ketamine infusion. Patient A was weaned from large doses of opioids and reported less pain. Patient B required escalating doses of opioids, other pain medications, and ketamine infusion in order to achieve moderate pain control. When pain became more severe, ketamine may be less useful in these patients and the mechanism of pain was different in these patients. Ketamine is useful in treating neuropathic pain and can help decrease opioid requirements which allows more effective analgesia as well as several consult services. If the progression of disease is causing more pain, ketamine may be more useful in these patients and palliative treatment modalities or radiation may be more efficacious. This may explain the lack of response to ketamine from patient B. Ketamine is successfully used in some cancer patients to treat moderate to severe neuropathic pain and increase opioid requirements but there is not enough available evidence to make specific recommendations for this population. Our case report highlights the heterogeneity of cancer pain and the need for additional studies to adequately assess risk vs benefit of this therapy according to a recent Cochrane review. The results of the RCTs included in the review found ketamine reduced pain intensity or reduced the dose of opioid needed, however the studies were too small to draw any definitive conclusions. 28 of the 32 case studies included in the review reported improved analgesia with ketamine. Results were mixed and a specific statement of “complete relief of pain”. None of the studies in the review included pediatric patients. One randomized, double blind study found no benefit from ketamine in treating cancer pain compared with placebo. The number needed to treat was 25 compared with number needed to harm was 1. Central side effects of ketamine include hallucinations, insomnia, drowsiness, and confusion. There was one report of subpial vascular myelopathy found postmortem following continuous intrathecal ketamine infusion. The brain levels of ketamine and norketamine from ketamine can be beneficial in preventing and treating side effects. Ketamine may be administered intravenously, intrathecally, intramuscularly, subcutaneously, sublingually, orally and rectally. The latter two routes are affected by first pass metabolism which decreases bioavailability by approximately 20% but has fewer side effects compared to IV. Ketamine is metabolized to norketamine in the liver and then excreted.