Use of Low-dose Ketamine Infusion for Pediatric Patients With Sickle Cell Disease-related Pain

A Case Series

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CASE REPORT

Objectives: Sickle cell disease-related pain is difficult to treat adequately. Pain secondary to vasoocclusive episodes (VOE) may be unresponsive to high-dose intravenous opiates. Alternative treatment options for VOE are needed. We sought to review our experience with low-dose ketamine for children hospitalized with VOE.

Methods: Retrospective medical chart reviews were conducted for hospitalized patients treated with ketamine for sickle cell VOE. Data gathered included vital signs, pain scores, opiate utilization, and adverse events.

Results: Five children and adolescents received a low-dose ketamine infusion for the treatment of sickle cell-related pain. Four received the infusion in addition to opiates (delivered via patient controlled analgesia) as a rescue intervention after several days of inadequate pain relief and 1 patient received ketamine in place of opiates. Two of the 5 patients achieved what seems to be clinically significant pain control with a low-dose ketamine infusion, whereas 1 additional patient had significant reduction in opiate utilization.

Discussion: Further research into ketamine for vasoocclusive pain is warranted.

Key Words: sickle cell disease, ketamine, vasoocclusive pain

Acutely severe pain episodes associated with sickle cell disease (SCD) are very difficult to manage effectively.1–5 Current therapies for pain in children with SCD are inadequate, resulting in marked under treatment of pain. Many children have vasoocclusive pain that is refractory to the analgesic effects of high-dose opiates and report severe pain for days to weeks after the onset of the episode.6–8 Recurrent or prolonged use of opiates, as is common in SCD, results in opiate tolerance, where a progressive increase in the dose of opiate is required to provide the same amount of symptomatic relief. A recent Cochrane review pointed to limited evidence for the efficacy of analgesic interventions in acute pain episodes of SCD.9

Ketamine, a NMDA receptor antagonist, is a dissociative anesthetic that has potent analgesic properties and can also prevent the development of opioid tolerance.10–12 In subanesthetic doses, ketamine can facilitate better pain relief in conjunction with lower doses of opiates in patients with severe pain such as those with postoperative, neuropathic,13–16 and end-of-life cancer pain. Ketamine has been used with success for pain control in children with cancer-related end of life pain in our own experience and also in the literature.17–19 In this population ketamine can provide excellent analgesia in the setting of severe pain, which is unresponsive to high doses of opiates, whereas reducing opiate-related side effects, that is, sedation, and preserving quality of life. Ketamine has also been used after surgical procedures such as appendectomies and spinal fusions,20,21 and its efficacy and safety for procedural sedation, most commonly in the emergency department, in children and adolescents has been well documented.22–31 In these patients ketamine provides excellent analgesia with limited respiratory depression.

Given that children with SCD can present with opiate unresponsive pain and experience opiate-related adverse events, ketamine, as a low-dose infusion, may be a useful adjunct in this population. We present a case series of 5 children with SCD who received low-dose ketamine infusions while hospitalized for vasoocclusive pain.

MATERIALS AND METHODS

Retrospective chart reviews were performed for the 5 patients with SCD who were hospitalized for vasoocclusive pain and received ketamine at our institution between June 22, 2006 and October 20, 2007. The Institutional Review Board approved this study and the need for informed consent was waived. Health Insurance Portability and Accountability Act (HIPAA) authorization was obtained from the patient’s parent or legal guardian before the chart review. Data collected from each hospitalization included demographic information (age, sex, race), medical history related to SCD (genotype, history of acute chest syndrome, splenic sequestration, or stroke, hydroxyurea, chronic transfusion therapy), initial presentation (admission source, number of days with pain, pain sites), vital signs, self-reported pain intensity scores, opiate utilization (type, total dose received, day of transition to oral opiates), ketamine utilization (rate, infusion duration and total dose received), use of nonsteroidal anti-inflammatory drugs (NSAIDs), and duration of hospitalization. Drug related adverse events were recorded. Charts were reviewed for adverse effects caused by ketamine including sedation, nyctagmus, agitation, hallucinations, and dysphoria; however, clinical...
staff did not receive instructions on recording ketamine-specific adverse events at the time of the infusion. Vital signs were evaluated for potential drug related changes by comparing the mean vital signs for each individual patient before during and after ketamine infusion.

RESULTS

Patients

On the basis of recent success with a low-dose ketamine in several patients with cancer-related end-of life pain 5 patients were offered a continuous ketamine infusion for vasoocclusive pain. Patients received ketamine after discussion regarding its risks and benefits between the hematology/oncology attending, the pain service, and the parents and/or patient. Four of the patients were selected for ketamine use several days into hospitalization, because of lack of response to traditional therapy (opiates delivered by patient-controlled analgesia). These patients received ketamine adjunctively. One patient received ketamine in lieu of opioids due to a failure to respond to opioids during several recent hospitalizations. The mean age was $13.4 \pm 2.96$ years (range: 10 to 18 y). Patient demographics are presented in Table 1. All patients were hospitalized for a primary diagnosis of sickle cell pain [sickle cell anemia with vasoocclusive pain (282.62), or sickle cell thalassemia with crisis (282.42)].

Ketamine Infusion

The starting dose of ketamine ranged from 0.06 mg/kg/h to 0.1 mg/kg/h. Titration of the ketamine infusion was based on patients pain score, adverse events, and attending preference. The ketamine infusion was increased no more frequently than every 4 hours with a maximum increase of $0.05$ mg/kg/h. The maximum ketamine infusion was limited to $0.2$ mg/kg/h. Two patients received a $0.1$ mg/kg bolus of ketamine before infusion initiation. Duration of the continuous infusion ranged from 19 to 90 hours (Table 2). Pain scores and opiate consumption before, during, and after the ketamine infusion are presented in Table 3. Intravenous (IV) opiate consumption during and outside of the ketamine infusion was similar for 3 of the patients who received IV opiates, with 1 patient requiring less opiates during the ketamine infusion (patient 5).

Ketamine as Rescue Intervention

Four patients received ketamine after several days of inadequate pain relief on IV opioids delivered via patient controlled analgesia. The patients were given ketamine as an adjuvant to their patient-controlled opiate regimen of either morphine or hydromorphone. One patient (patient 5) had dramatic reduction in her headache symptoms after the onset of the ketamine infusion. The other 3 did not have clear improvement in pain relief; however, patient 1 used considerably less opiate during the infusion of ketamine.

Ketamine Alone

One patient (patient 3) received low-dose ketamine infusion as the only analgesic for her vasoocclusive episode. The patient received ketamine within 2 hours of hospitalization at a dose of $0.1$ mg/kg/h for a total of 25 hours. Although this patient’s pain score was low at the time of hospitalization, this was typical of her usual presentation. Her pain scores did decrease during the ketamine infusion. The infusion was discontinued when she reported adequate pain relief. Her hospitalization duration was at least 24 hours shorter than her 4 previous hospitalizations all of which had occurred within the previous 12 months. This patient also had a decrease in her average heart rate during the infusion, which may represent better pain control (Table 4).

Adverse Events

Two patients had adverse events. One of these patients complained of dysphoria after the initial bolus, and this dysphoria remained while she was on the continuous infusion. She asked that the ketamine be discontinued after 19 hours. The other patient developed unexpected nystagmus, hypertension, and unresponsiveness when a new

<table>
<thead>
<tr>
<th>Patient</th>
<th>Hospital Day</th>
<th>Started Ketamine</th>
<th>Ketamine Starting Dose (mg/kg/h)</th>
<th>Highest Dose of Ketamine (mg/kg/h)</th>
<th>Total Infusion Duration (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td></td>
<td>0.06</td>
<td>0.18</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td></td>
<td>0.1 + 0.1 mg/kg bolus</td>
<td>0.2</td>
<td>24</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td></td>
<td>0.1</td>
<td>0.1</td>
<td>25</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td></td>
<td>0.1 + 0.1 mg/kg bolus</td>
<td>0.2</td>
<td>19</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td></td>
<td>0.1</td>
<td>0.2</td>
<td>90</td>
</tr>
</tbody>
</table>

F indicates female; HgbSS, homozygous sickle hemoglobin disease; M, male; N, no; SCD, sickle cell disease; Y, yes.
infusion of ketamine was begun, 24 hours after the initial infusion. He did not have these symptoms before the change in ketamine solution. Staff members felt this patient likely received an inadvertent bolus of ketamine during the transition to the new infusion. None of the other patients or the clinical staff caring for these patients noted any adverse events during their infusions.

Mean pulse and systolic blood pressures before, during, and after ketamine are shown in Table 4. Three patients had decrease in average heart rate and one patient’s average heart rate increased while on ketamine. Three patients had increases in blood pressure during the infusion and in one (patient 4) this did reach the borderline hypertensive range. None of these patients had clinical symptoms associated with these vital sign changes. There were not clinically relevant changes in the average temperature, respiratory rate, oxygen saturation, or diastolic blood pressure in any patient during the ketamine infusion.

DISCUSSION

This case series represents the first published data on the use of low-dose ketamine as a treatment for vasoocclusive pain in SCD. In this case series, 2 of 5 patients achieved what seems to be clinically significant pain control with a low-dose ketamine infusion. One of these patients received ketamine as an adjunct to opiate therapy and the other received it as the primary analgesic agent. An additional patient had a marked reduction in opiate utilization during ketamine infusion; however, she did not indicate improved pain relief. Notably, the patient with the most significant change in pain score (patient 5) was on considerably more opiate than the other patients suggesting ketamine may be more effective at higher opiate levels or in those who are opiate tolerant or have opiate-related hyperalgesia. A similar situation occurs in the use of ketamine in cancer-related end of life pain.

Recent studies suggest that central sensitization and the development of opioid tolerance play significant roles in acute, severe pain states. Central sensitization results when a noxious stimulation leads to the opening of NMDA receptors and hyperexcitability of dorsal horn neurons, leading to increased sensations of pain and hyperalgesia. Opioid tolerance develops via activation of the NMDA receptors as well, resulting in the down-regulation of opioid receptors.

Previous research suggests that ketamine may be able to prevent the development of opioid tolerance, reduce central sensitization and facilitate better pain relief with lower opiate doses. Given that central sensitization and opiate tolerance may play a significant role in

### TABLE 3. Pain Scores and Opiate Utilization

<table>
<thead>
<tr>
<th>Patient</th>
<th>Before Ketamine Infusion</th>
<th>During Ketamine Infusion</th>
<th>After Ketamine Infusion</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pain score* 8.9</td>
<td>10</td>
<td>8.6</td>
<td>Ketamine discontinued due to lack of efficacy</td>
</tr>
<tr>
<td></td>
<td>Opiate use† 0.07 mg/kg/h</td>
<td>0.03 mg/kg/h</td>
<td>0.04 mg/kg/h</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Pain score 7.6</td>
<td>7.2</td>
<td>5.7</td>
<td>Nystagmus, unresponsive, agitation, increased blood pressure following the start of a new bag</td>
</tr>
<tr>
<td></td>
<td>Opiate use 0.07 mg/kg/h</td>
<td>0.06 mg/kg/h</td>
<td>0.06 mg/kg/h</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Pain score 3</td>
<td>2.9</td>
<td>2.2</td>
<td>Achieved adequate pain control</td>
</tr>
<tr>
<td></td>
<td>Opiate use Did not require intravenous opiates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Pain score 7.9</td>
<td>7.5</td>
<td>7.1</td>
<td>Patient did not like feeling of ketamine; complained of feeling dysphoric and asked to be taken off</td>
</tr>
<tr>
<td></td>
<td>Opiate use 0.06 mg/kg/h</td>
<td>0.06 mg/kg/h</td>
<td>0.06 mg/kg/h</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Pain score 10</td>
<td>4.6</td>
<td>2.8</td>
<td>Achieved adequate pain control</td>
</tr>
<tr>
<td></td>
<td>Opiate use 0.17 mg/kg/h</td>
<td>0.21 mg/kg/h</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>

*Zero to 10 Numerical Rating Scale.† Intravenous (IV) morphine or hydromorphone calculated in morphine equivalents.

### TABLE 4. Vital Sign Trends

<table>
<thead>
<tr>
<th>Patient</th>
<th>Average Pulse (Beats/Min)</th>
<th>Average Systolic BP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-Ketamine</td>
<td>During Ketamine</td>
</tr>
<tr>
<td>1</td>
<td>84.8</td>
<td>76.6</td>
</tr>
<tr>
<td>2</td>
<td>107.5</td>
<td>108.7</td>
</tr>
<tr>
<td>3</td>
<td>102.0</td>
<td>74.7</td>
</tr>
<tr>
<td>4</td>
<td>102.9</td>
<td>114.8</td>
</tr>
<tr>
<td>5</td>
<td>95.2</td>
<td>83.1</td>
</tr>
</tbody>
</table>
vasoocclusive pain, ketamine could represent an effective treatment alternative or adjunct for those with sickle cell pain. Certainly, the safety of ketamine must be ensured if it is to be used as an adjunctive analgesic in vasoocclusive pain. In the anesthetic doses, adverse effects could include apnea with rapid IV administration, increased salivation, nausea/vomiting, hypotension, and increased intracranial pressure. Occasionally, patients complain of hallucinations or strange dreams, especially upon emergence from ketamine anesthesia. However, 21 of 37 perioperative trials of low-dose ketamine did not report any psychomimetic side effects such as hallucinations, disorientation, or dysphoria. Doses of ketamine, lower than 150 µg/kg/h are rarely associated with psychomimetic side effects. Additionally, in contrast to opiates and other sedatives, ketamine maintains airway effects. Additionally, in contrast to psychomimetic side effects of ketamine, lower than 150 µg/kg/h are rarely warranted. of ketamine in patients with vasoocclusive pain are given the findings of our case series, future investigations of these are clearly di.

According to the study, Hallucinations, disorientation, or dysphoria. Occasionally, patients complain of hallucinations or strange dreams, especially upon emergence from ketamine anesthesia. However, 21 of 37 perioperative trials of low-dose ketamine did not report any psychomimetic side effects such as hallucinations, disorientation, or dysphoria. Doses of ketamine, lower than 150 µg/kg/h are rarely associated with psychomimetic side effects. Additionally, in contrast to opiates and other sedatives, ketamine maintains airway reflexes and respiratory drive. Two of our patients experienced unacceptable side effects which led to the discontinuation of the infusion. These side effects occurred as the result of either intentional or inadvertent bolus dosing. This should be avoidable in the future. No patient had changes in vital signs, which led to discontinuation of the infusion. Given the retrospective nature of our case series some adverse effects caused by ketamine might not have been identified. Despite the advent of more aggressive treatment regimens, sickle cell pain remains a most challenging clinical problem. For many patients with SCD, opiates alone do not lead to improvement in symptoms. Our previous experience with low-dose ketamine in cancer-related end of life pain led us to hypothesize that ketamine might be beneficial to those children hospitalized with vasoocclusive pain. Although these are clearly different clinical scenarios there are some overlapping themes. Both groups represent extremely challenging situations where common therapies have been ineffective and cause many unacceptable side effects.

Although our case series provides limited information regarding the efficacy of ketamine in sickle cell pain, 3 of the patients had changes in status (either decrease in pain score or decrease in opiate utilization) during the infusion. Given the findings of our case series, future investigations of ketamine in patients with vasoocclusive pain are warranted.

REFERENCES


