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5 2 Short-Term Lidocaine Infusion as a Non-Sedative Option to Maintain Ventilator
6 3 Synchrony during Opioid Taper in a COVID-19 Patient
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1 Introduction

2 During the final months of 2019, a novel pathogen called Severe Acute Respiratory
3 Syndrome Coronavirus 2 (SARS-CoV-2) emerged with an associated disease known as
4 Coronavirus disease 2019 (Covid-19). Patients infected with Covid-19 manifested varying levels
5 of severity, and patients afflicted with severe disease often required admission to the Intensive
6 Care Unit (ICU) with prolonged sedation to facilitate mechanical ventilation.

7 Patients admitted to the ICU are especially prone to painful stimuli from prolonged
8 immobilization, invasive catheters, procedures, and inflammation from the ongoing critical
9 illness [1, 2]. Intubated and sedated patients may be unable to communicate their discomfort,
10 and a failure to adequately treat their pain can lead to future complications such as
11 cardiomyopathy, anxiety, or post-traumatic stress disorder [1]. Thus, ICU consensus guidelines
12 endorse the analgosedation strategy, in which opioid analgesics are the primary method for
13 maintenance of both analgesia and sedation [3, 4]. Intubated patients undergo spontaneous
14 breathing trials (SBT) to predict their readiness for eventual extubation. During the SBT,
15 ventilator-support is minimized and medications that inhibit the respiratory drive, such as
16 opioids, are briefly withheld. SBT assessment can assist in determining if a patient is ready for
17 ventilator liberation and can dictate when a patient is extubated.

18 In the following case, we describe a patient with Covid-19 induced respiratory failure
19 who required prolonged intubation and ventilatory support. The extended duration of opioid-
20 based analgosedation led to the development of an opioid tolerance and associated difficulty
21 weaning off the patient's opioid regimen. We describe the use of short-term lidocaine infusion
22 to maintain adequate analgesia and ventilator synchrony during high dose opioid taper.

1 Case Description

2 In June of 2020, a 61 year old, opioid-naïve female with no significant past medical
3 history presented to her local Emergency Department in acute hypoxic respiratory distress. She
4 was initially placed on BiPAP (100% FiO₂) but was subsequently intubated due to persistent
5 hypoxia. Chest x-ray obtained in the ED revealed diffuse lung opacities suspicious for COVID-
6 19 Pneumonia. She was transferred to a tertiary care ICU for advanced care measures based on
7 her presumed diagnosis, which was later confirmed to be Covid-19. In the coming days, she
8 would endure a prolonged hospitalization aggravated by complications including a type 2 non-
9 ST elevation myocardial infarction (NSTEMI), renal failure necessitating continuous renal
10 replacement therapy (CRRT), and the development of opioid tolerance which eventually led to
11 an iatrogenic opioid withdrawal syndrome.

12 When the patient was first admitted to the ICU, she was started on a continuous fentanyl
13 infusion for both sedation and analgesia. Her sources of pain included inflammation from
14 critical illness itself, endotracheal intubation, placement of multiple invasive catheters such as
15 arterial and central access lines, urinary catheter placement, three bronchoscopies, and other
16 routine procedures in the ICU. Due to concern for excess fluid intake, the patient was switched
17 from fentanyl to a more concentrated hydromorphone infusion on admission day 5. Early in her
18 hospital course she tolerated pausing opioid infusions to attempt SBTs. However, trials to assess
19 her readiness for ventilator liberation were unsuccessful and so a planned tracheostomy was
20 placed on day 31.

21 As her hospitalization progressed, she required higher opioid doses to remain sedated.
22 On hospitalization day 41 another sedation holiday and SBT was attempted. However, cessation
23 of the hydromorphone infusion resulted in the patient experiencing diarrhea, tachycardia,

1 hypertension, and worsened ventilator dyssynchrony. These symptoms only resolved after
2 resuming the opioid infusion. Based on these findings, it was presumed the patient was
3 exhibiting signs of opioid withdrawal and so a gradual opioid taper was initiated. A
4 pharmacological cocktail consisting of alpha-2 agonists, antidiarrheals, and a ketamine infusion
5 (up to 1.5mg/kg/hr) was used in an attempt to manage the physiologic aberrations observed
6 during opioid weaning, yet the patient continued to grimace and show signs of agitation with
7 breakthrough hypertension, tachycardia, and ventilator dyssynchrony. The ICU team felt that the
8 patient's agitation and physiologic changes were nonspecific for either opioid withdrawal or
9 inadequate analgesia, and likely represented a contribution from both etiologies. Thus, on
10 admission day 45, the Inpatient Pain Medicine Service were consulted for further pain
11 management recommendations.

12 At the time of this consult, the patient was on approximately 1160 OME with a ketamine
13 infusion at 1.5 mg/kg/hr (Figure 1). The pain medicine team considered options such as
14 methadone, a remifentanyl infusion, or a lidocaine infusion as a method to control the patient's
15 pain while tapering hydromorphone. Given that the opioid receptors were likely saturated, and
16 that the patient was already receiving an NMDA-antagonist, an alternative mechanism for non-
17 sedative analgesia bypassing both pathways was deemed most appropriate. Hence, the decision
18 was made to initiate a lidocaine infusion. The lidocaine infusion was used for a total of 5 days,
19 with a rate of 1 mg/kg/hr for the first 4 days and 0.5mg/kg/hr for the final day. To avoid local
20 anesthetic systemic toxicity, serum lidocaine levels and ECGs were evaluated. Three serum
21 lidocaine levels were checked, with a Day 1 level of 2.4 mcg/ml, Day 3 level of 1.8 mcg/ml, and
22 Day 4 level of 2.1 mcg/ml which were all within therapeutic range. Routine daily ECGs showed
23 no concerning deviations from baseline during the infusion period. After 5 days (admission days

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3 1 45-49) of continuous lidocaine infusion while drastically tapering opioids, the patient's
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5 2 hydromorphone infusion was discontinued and she was only maintained on intermittent doses of
6
7 3 enteral hydromorphone, without signs of opioid withdrawal. Her daily OME had decreased by
8
9 4 roughly 90% from 1160 to 120 OME mg, and so the lidocaine was discontinued after a 5 day
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11 5 infusion. Additionally, given the success of the lidocaine infusion in managing the patient's pain
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13 6 during opioid reduction, the ketamine infusion had been discontinued on day 47. After her
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15 7 opioid dose had been significantly reduced, she successfully tolerated daily spontaneous
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17 8 breathing trials without further evidence of ventilator desynchrony or signs concerning for opioid
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19 9 withdrawal.
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25 10 The patient transferred to an LTAC on hospital day 59 and after further convalescence,
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27 11 she was discharged home without opioid prescriptions and has since returned to her normal state
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29 12 of health.
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16 **Figure 1:** Opioid use trend in a mechanically ventilated COVID-19 patient requiring prolonged
17 sedation. X-axis denotes day in the ICU and Y-axis denotes daily opioid requirements in oral
18 morphine equivalents (OME mg). A contracted course is displayed on this graph to emphasize
19 the trend around the period of lidocaine infusion initiation (red circle). She had been on
20 numerous sedative agents upon ICU admission including various forms of opioids at high doses.
21 A significant downtrend in OME was noted and maintained upon initiation of lidocaine infusion.

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1 Discussion

2 In the case described here, the patient is unable to communicate the subjective experience
3 of opioid withdrawal because she was intubated and mechanically ventilated. While the
4 literature suggests that the development of iatrogenic opioid withdrawal in ICU patients can be
5 anywhere from 16-30% [5-7], it can be difficult to discern a withdrawal syndrome from the
6 natural increase in sympathetic outflow that comes with decreased sedation. Despite the inability
7 to have our patient endorse the subjective symptoms of opioid withdrawal, she did still fulfill the
8 DSM-V criteria for opioid withdrawal by having agitation, diarrhea, and a fever shortly after
9 opioid dose reduction [5]. Our diagnosis of iatrogenic opioid withdrawal was further
10 strengthened by the temporal relationship between a reduction in opioids shortly followed by the
11 patient manifesting the aforementioned symptoms. Finally, it was telling that our ICU
12 colleagues, who routinely wean patients from opioid based sedation, strongly felt that this was a
13 true opioid withdrawal presentation.

14 Our pain medicine service agreed with the ICU team that the patient was experiencing
15 opioid withdrawal; however, we were also concerned about the potential for opioid-induced
16 hyperalgesia . Patients who receive prolonged opioid infusions can develop a paradoxical
17 increased perception of pain to a stimulus termed opioid-induced hyperalgesia [8]. Our patient
18 was especially at risk for opioid-induced hyperalgesia due to her prolonged opioid infusion,
19 along with other risk factors including an active infection, heightened stress-response, and
20 chronic inflammation [2, 8]. Additionally, opioid withdrawal hyperalgesia could have also
21 contributed to inadequate analgesia during the initial phase of the opioid taper.

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3 1 When the pain medicine team was consulted, the patient was being weaned from
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5 2 hydromorphone while receiving dexmedetomidine to treat the physiologic symptoms of opioid
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7 3 withdrawal and ketamine as a replacement analgesic. Despite high dose (1.5 mg/kg/hr) ketamine
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9 4 infusion, our patient remained unable to tolerate opioid weaning and the ICU team expressed
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11 5 concerns about inadequate analgesia. Thus, we recommended initiating lidocaine infusion as an
12
13 6 alternate analgesic modality. Methadone, which has been used successfully as an analgesic
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15 7 bridge during high dose opioid taper was considered, but was avoided due to the patient's
16
17 8 tenuous cardiac status and methadone's sedative properties.
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22 9 The decision to utilize a lidocaine infusion to achieve analgesia while weaning opioids
23
24 10 was based on previous evidence where it has been shown to be effective as an adjunctive
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26 11 analgesic in ICU patients [9]. The duration and dose of lidocaine used in this case was based on
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28 12 derivative evidence for acute post-operative and refractory cancer-related pain [10]. Further,
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30 13 evidence suggests that patients with chronic opioid use have superior pain control with lidocaine
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32 14 instead of ketamine [10]. Serum lidocaine levels were monitored to maintain therapeutic levels
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34 15 and minimize the risk of local anesthetic systemic toxicity. Finally, while this case demonstrated
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36 16 lidocaine's efficacy as a substitute analgesic during opioid taper; lidocaine is not without risk and
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38 17 further research is warranted.
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3 1 Questions
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- 6 2 1. A potential complication of intravenous lidocaine use is local anesthetic systemic toxicity
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8 (LAST), it can be treated with which of the following medications?
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10 a. Amiodarone
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12 b. Intralipid
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14 c. Methylene blue
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16 d. Dantrolene
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18 e. Calcium gluconate
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23 9 Answer: B Intralipid, specifically 20% Intralipid, is used as the treatment for LAST. A 1.5
24 10 mL/kg bolus is given initially, which is followed by an infusion at 0.25 ml/kg/min for 30-60
25 11 minutes.
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- 31 13 2. Signs and symptoms of opioid withdrawal may be difficult to observe in a patient who is
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33 14 intubated and mechanically ventilated, which of the following is not an expected
34
35 15 manifestation of opioid withdrawal?
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37 a. Mydriasis
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39 b. Diarrhea
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41 c. Hypertension
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43 d. Tachycardia
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45 19 e. Miosis
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50 21 Answer: E Miosis. Miosis, or pupillary constriction, is a well-established sign of opioid overdose
51 22 or intoxication. The other listed signs including mydriasis (pupillary dilation), hypertension,
52 23 tachycardia and diarrhea are typically associated with acute opioid withdrawal.
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3 1 Disclosures
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6 2 None
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89 3 References
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- 12 4 1. Barr, J., et al., *Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit*. Critical Care Medicine, 2013. **41**(1): p. 263-306.
- 13 5 2. Martyn, J.A.J., J. Mao, and E.A. Bittner, *Opioid Tolerance in Critical Illness*. New England Journal of Medicine, 2019. **380**(4): p. 365-378.
- 14 6 3. Karamchandani, K., et al., *Challenges in Sedation Management in Critically Ill Patients with COVID-19: a Brief Review*. Current Anesthesiology Reports, 2021.
- 15 7 4. Devabhakthuni, S., et al., *Analgo-sedation: a paradigm shift in intensive care unit sedation practice*. Ann Pharmacother, 2012. **46**(4): p. 530-40.
- 16 8 5. Wang, P.P., et al., *Opioid-associated iatrogenic withdrawal in critically ill adult patients: a multicenter prospective observational study*. Ann Intensive Care, 2017. **7**(1): p. 88.
- 17 9 6. Hyun, D.-g., et al., *Iatrogenic Opioid Withdrawal Syndrome in Critically Ill Patients: a Retrospective Cohort Study*. J Korean Med Sci, 2020. **35**(15).
- 18 10 7. Cammarano, W.B., et al., *Acute withdrawal syndrome related to the administration of analgesic and sedative medications in adult intensive care unit patients*. Crit Care Med, 1998. **26**(4): p. 676-84.
- 19 11 8. Lee, M., et al., *A comprehensive review of opioid-induced hyperalgesia*. Pain Physician, 2011. **14**(2): p. 145-61.
- 20 12 9. Kandil, E., E. Melikman, and B. Adinoff, *Lidocaine Infusion: A Promising Therapeutic Approach for Chronic Pain*. J Anesth Clin Res, 2017. **8**(1)
- 21 13 Mo Y, Thomas MC, Antigua AD, Ebied AM et.al. Continuous Lidocaine Infusion as Adjunctive Analgesia in Intensive Care Unit Patients. J Clin Pharmacol. 2017 Jul;57(7):830-836.
- 22 14 10. Sahmeddini, M.A., M.B. Khosravi, and A. Farbood, *Comparison of Perioperative Systemic Lidocaine or Systemic Ketamine in Acute Pain Management of Patients With Opioid Use Disorder After Orthopedic Surgery*. J Addict Med, 2019. **13**(3): p. 220-226.
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Lidocaine Infusion as a weaning modality for Prolonged Intubation from COVID-19 Pneumonia Complicated by Iatrogenic Opioid Withdrawal Syndrome

