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Letter to the Editor

Ketamine infusion for pain management in hospitalized patients with Chronic Pancreatitis: A case series

To the editor,

Chronic pain is a major determinant for healthcare utilization and decreased quality of life in patients with Chronic Pancreatitis (CP). CP patients suffering from chronic pain often require opioids or neuromodulating medications as an outpatient [1,2]. Pain control during inpatient admission also poses a significant challenge for providers and inpatient opioid use may lead to dependence as an outpatient [3]. A subset of patients undergo invasive procedures including surgery for pain management with variable results [4]. There is an obvious need to find alternative medications for management of painful CP.

Chronic opioid use can lead to hyperalgesia and dependence due to the activation of N-methyl-D-aspartate (NMDA) receptors, resulting in suboptimal response and increased risk of opioid-related adverse effects [5]. Ketamine, a noncompetitive NMDA receptor antagonist, has been used successfully in chronic pain associated with central sensitization such as complex pain syndrome and post-amputation limb pain [6,7], which has also been proposed to play a role in CP-related pain. Supraspinal mechanisms appear to play an important role in ketamine's ability to decrease the activation of pain pathways in multiple regions of the brain, though research is underway to better illuminate the involved mechanisms [8].

To date, ketamine use in patients with CP hospitalized with acute exacerbations of pain has been anecdotal as case reports [9,10]. In a study protocol published in 2015 on this topic, the investigators proposed to randomize 40 patients with painful CP to receive 8 h of intravenous S-ketamine followed by oral S-ketamine (vs. placebo) for 4 weeks. The primary end point was clinical pain relief as assessed by a daily pain diary while secondary end points included patient-reported outcome measures, opioid consumption and rates of side effects. However, this study has not been completed to date [11].

In this letter, we report our experience with ketamine infusion during an inpatient admission with painful CP. Our primary aim was to evaluate the feasibility and safety of ketamine infusion and secondary aims were the efficacy of ketamine for optimizing pain control, reducing the need for opioids and health care utilization. We retrospectively identified adult patients with CP through an electronic data search of the University of Pittsburgh Medical Center (UPMC) data systems who received ketamine infusion for management of pain during a pancreatitis-related inpatient admission between 2015 and 2020 at UPMC Presbyterian-Shadyside campus. Electronic health records were reviewed by two authors (FE, JE) under the supervision of senior authors (DY, TE) to abstract information on patient and relevant disease-related variables. We recorded information on opioid use, type and dose of opioid used prior to index hospitalization and average daily morphine equivalents (MME). We noted healthcare utilization within six months prior to and after the index hospitalization including the number of Emergency Department visits, pain-related hospitalizations and the duration of hospitalization. For the index admission, we recorded information on pain from nursing staff documentation. Our nursing staff document a visual analogue scale for pain every 6 hours in the electronic health records based on patient self-report (scale 0–10, with 10 being the most severe pain). Using this information, we calculated mean pain scores from the four readings each day. We noted opioid use prior to and after ketamine infusion, dose and duration of ketamine infusion and any adverse events related to ketamine use. Opioid medication use was converted to MME using a narcotic analgesic converter. At our institution, ketamine is typically ordered in a non weight-based format at 5 mg/hr or 10 mg/hr for 48 hours. At the 48-h point, the order is automatically discontinued unless the ordering physician renews the infusion for an additional 48 hours. We used the Wilcoxon Signed Rank test, a non-parametric alternative of the pairwise *t*-test, to test the null hypothesis of no difference in post-versus pre-measurement median values for pain for each patient at the significance level of 0.05.

During 2015–2020, 14 adult patients with CP received Ketamine infusion during hospitalization for pancreatitis-related pain. The median age (interquartile range, IQR) was 43 years (34, 66), 9 (64.3%) were female and all (100%) were white. History of prior or current smoking was reported by 9 (42.9%) and 2 (14.3%) patients, respectively. The etiology was alcohol in 4 (28.6%), idiopathic in 9 (64.3%) and hypertriglyceridemia in 1 (7.1%) patients. History of prior endoscopic therapy was noted in 6 (42.9%) and prior pancreatic surgery in 2 (14.2%) patients. Table 1 shows relevant data on pain, opioid use, healthcare utilization and ketamine infusion. Table 2 shows data on change post-versus pre-ketamine in the different variables of interest. A significant reduction in pain was noted after ketamine infusion (median of 6.9 vs. 8.93). No significant change was noted for opioid dosage (as mg or MME) and healthcare utilization after when compared to before ketamine infusion. Ketamine infusion was tolerated well except for one patient who reported hallucinations that resolved upon discontinuation of the ketamine infusion.

Our findings suggest that ketamine infusion can be safely administered and was well tolerated in patients hospitalized with painful CP. We also noted significant improvement in pain scores after ketamine infusion. The median duration of hospitalization

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Table 1
Select characteristics of the study population.

Variable	N = 14
Outpatient opioid use – n (%)	
Current	7 (50)
Past	4 (28.6)
Never	3 (21.4)
Current neuromodulating agent use – n (%)	4 (28.5)
History of pain blocks – n (%)	5 (35.7)
Hospital stay length in total (days) – median (IQR), [range]	7 (4, 9), [2, 30]
Total length of ketamine use (days) – median (IQR), [range]	1.5 (1, 2), [1, 2]
Total dose of ketamine administered (mg) – median (IQR), [range]	127.5 (83, 230), [25, 470]
Avg daily MME in mg (inpatient) – median (IQR), [range]	
Pre-ketamine infusion	36 (10, 76)
Post-ketamine infusion	38.75 (15.8, 87.3), [0, 150]
Average Pain score during index admission – median (IQR), [range]	
Pre-ketamine infusion	8.93 (8, 9.6), [3, 10]
Post-ketamine infusion	6.9 (6, 7.5), [3.8, 8.2]
Days of hospitalization – median (IQR), [range]	
Pre-ketamine infusion	2 (0, 4), [0, 7]
Post-ketamine infusion	3 (2, 5), [1, 21]
Ketamine side effects (Hallucinations) – n (%)	1 (7.1)
Healthcare utilization (6 months) – median (IQR), [range]	
Pre-ketamine infusion	0.5 (0, 4), [0, 8]
Post-ketamine infusion	1.5 (1, 3), [0, 6]
Average daily opioid use in mg – median (IQR), [range]	
3 months before index admission	63.75 (0, 80), [0, 150]
3 months after index admission	40 (, 83), [0, 150]

Table 2
Pairwise tests of post versus pre-Ketamine measurements within each patient.

Post-Pre Ketamine change	N = 14	Wilcoxon Singed rank test statistics (S)	p-value
Average Pain score	−1.95 (−2.3, 1.5) [-4.2, 1]	**−51.5**	**0.0002**
Average daily opioid (mg)	0 (0, 0)^ [-50, 90]	−1.5	0.8125
Average daily MME (in patient, mg)	0 (−24.2, 21.3) [-67.4, 110]	−1	0.9658
Health care utilization (days)	0 (0.00, 1.00) [-5, 4]	0	>0.99

^n = 13; median (IQR), [range].

after ketamine infusion was 3 days and no within patient difference was noted in the dosage of opioids or healthcare utilization before or after ketamine infusion. Due to the lack of a control arm, it is difficult to interpret or put these results into perspective as to whether ketamine use helps in reducing the need for opioids or duration of hospitalization, and opioids dosage and healthcare utilization during follow-up. In addition, ketamine is also used as an illicit substance and has abuse potential. Clinicians should therefore be diligent on patient selection and monitor the patient closely during its use. Future research should use a structured protocol for the dose and duration of ketamine infusion, criteria for use and dosing of opioids and adjunctive pain medications, and collection of outcomes data before and after ketamine infusion to determine if ketamine infusions help in improving clinical outcomes in patients hospitalized for painful CP.

Each change measure was computed by post - pre (so negative value indicates a decreased measure, while a positive value represents an increase in the measure). The Wilcoxon Signed Rank test was used to compare the median of the pre and post measures within patient and test the hypothesis of no post-pre difference at the significance level of 0.05.

Declaration of competing interest

None (FUE, JE, MS, CK DY).
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Point by point rebuttal

Editorial comment

Please refer to a recent study in Pancreatology (Parhiala M et al.; Scandinavian Baltic Pancreatic Club. Surgical strategies for chronic pancreatitis in a 1327- patient Scandinavian Baltic pancreatic Club (SBPC) register. Pancreatology. 2023 Jan; 23(1):28–34) in the beginning of the letter.

We appreciate comment from the editor. We included this relevant reference in the beginning of the letter as below.

A subset of patients undergo invasive procedures including surgery for pain management with variable results [4].

Reviewer #1: The letter by Ertem et al. describes a case series on the use of ketamine in patients with chronic pancreatitis admitted with acute painful episode. The letter provides a new therapeutic option for pain management in chronic pancreatitis which is safe though they had used it for 48 hours only. Ketamine is also a recreational drug and has abuse potential. The authors should mention it and advise to exercise caution regarding its repeated or prolonged use.

We agree with Reviewer #1 that this important point about ketamine's potential abuse should be mentioned in the discussion section of the letter therefore, we added the text as below.

In addition, ketamine is also used as an illicit substance and has abuse potential. Clinicians should therefore be diligent on patient selection and monitor the patient closely during its use.

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