PART B
STUDY DESCRIPTION

TITLE OF PROTOCOL	USE OF PATIENT CONTROLLED ANALGESIA FOR TREATING THE PAIN OF ACUTE PANCREATITIS: A PROSPECTIVE STUDY
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B1. PURPOSE OF PROTOCOL

This study aims to compare the efficacy of and outcomes in patients with acute pancreatitis (AP) receiving patient-controlled analgesia (PCA) with those receiving traditional physician-directed analgesia (PDA).

B2. SIGNIFICANCE AND BACKGROUND FOR THE STUDY

AP represents a critical health concern nationwide, with estimated 274,000 admissions annually and at a cost of 2.6 billion dollars. Current treatment strategies for AP are limited to supportive care with fluid resuscitation, analgesia, nutrition and prevention of end organ damage. Abdominal pain is often the predominant symptom in patients with AP and is treated with analgesics. As there is currently no disease-specific medical treatment to change the natural history of pancreatitis, pain control remains central to the treatment of AP (1). Among the analgesics, opioids have been shown to be provide safe and effective pain control in patients with AP. Current literature shows that there is no difference in the risk of pancreatitis complications or clinically serious adverse events between opioids and other analgesia options (2). Among hospitalized AP patients, adequate pain control often requires the use of intravenous (IV) opiates in the first 24-48 hours, which can later be transitioned to oral (PO) opioids. While there are various methods of delivering opioid medications such as IV, PO, and transdermal to name a few, IV opioids are commonly administered, either on a scheduled and/or on an as needed (PRN) basis as directed by the attending physician. In contrast to the conventional, method of physician directed IV opioid delivery, PCA is a form of IV opioid medication delivery in which the patient can rapidly titrate the opioid dose to manage variable levels of pain (3). This modality of opioid administration is often preferred by patients and has been widely used in postsurgical and obstetric patients to effectively treat their pain (4-6). PCA allows for faster intervention on pain limiting time to treatment and peak pain levels and has also been shown to decrease total opioid dose. However, there is limited evidence in published literature assessing the feasibility of using PCA to treat the pain of AP or comparing its efficacy and safety profile compared to the more traditional physician directed analgesia. One retrospective study has shown that use of PCA was surprisingly associated with longer hospital stays and higher rates of outpatient opioid use when compared to PDA, however there are no prospective trials to study this comparison (7). Hence, in this study, we compare the effects of using PCA among patients with AP to that of conventional PDA.

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B3. DESCRIPTION OF RESEARCH PROTOCOL

A. Study Design – Overview, Methods, Procedures

- We will identify patients with AP based on the 2012 revised Atlanta criteria for diagnosis, i.e., AP is diagnosed if 2 out of the following 3 criteria are met:
- Acute onset of persistent, severe, epigastric pain often radiating to the back,
- Elevation in serum lipase or amylase to three times or greater than the upper limit of normal,
- Characteristic findings of acute pancreatitis on imaging (contrast-enhanced computed tomography [CT], magnetic resonance imaging [MRI], or transabdominal ultrasonography).
- Patients will be recruited for participation in this study while they are hospitalized with AP at Beth Israel Deaconess Medical Center. Once the patient has been transferred from the ED to the hospital floor, we will identify and recruit them for participation in our study.
- After obtaining informed consent from the patient, the patient will be enrolled by simple randomization to either the PCA or the PDA arm of the study. The research staff will assign patients to either the PCA arm or the PDA arm based on a standard randomization. Once, a patient has consented, the research staff will assign them to the next sequential study ID and corresponding study arm and let the attending hospitalist know of the result. The patient will then be enrolled in their assigned arm.

- The initial protocol for analgesic administration in each arm is as follows:

- **Recommended algorithm for physician directed analgesia (PDA) arm:**
  - IV Hydromorphone 0.4 mg Q4H PRN for pain 4-6
  - IV hydromorphone 0.6 mg Q2H PRN for pain 7-10
  - Rescue IV hydromorphone 0.4 mg Q2H PRN for pain 4-10 = only to be given as a 'rescue dose' if patient has persistent pain despite using Q4H PRN IV hydromorphone (breakthrough pain)
  - Maximum opioid dosing: 1 mg per hour and 3 mg of IV hydromorphone per 4 hours
  - If patient has received more than 2 rescue doses for breakthrough pain in 12 hours or is in uncontrolled pain: Hospitalist's recommended step-up orders: IV hydromorphone 0.8 mg Q4H PRN 4-6

- **Recommended algorithm for patient controlled analgesia (PCA) arm:**
  - IV Hydromorphone 0.1 mg Q10 minutes
  - Rescue IV hydromorphone 0.4 mg Q2H PRN for pain 4-6, hydromorphone 0.6 mg Q2H PRN for pain 7-10 = only to be given as a 'rescue' dose for if patient has persistent pain despite using PCA (breakthrough pain)
  - Maximum opioid dosing: 1 mg per hour and 3 mg of IV hydromorphone per 4 hours
  - If patient has received more than 2 rescue doses for breakthrough pain in 12 hours or is in uncontrolled pain: Hospitalist's recommended step-up orders: IV hydromorphone 0.2 mg Q10 minutes

- **Recommended for all patients:**
  - PO Acetaminophen 1000 mg Q8H scheduled

- IV Naloxone 40-80 mcg PRN for respiratory depression (RR<10) or significant somnolence
- PO Benadryl 25mg Q4H PRN moderate to severe pruritis

- **Recommended algorithm for transition to oral:**
- PO Oxycodone 5mg Q4H PRN for pain 4-6
- PO Oxycodone 10mg Q4H PRN for pain 7-10
- Rescue PO Oxycodone 5mg Q2H PRN for pain 4-10 = only to be given as a 'rescue dose' if patient has persistent pain despite using Q4H PO oxycodone (breakthrough pain)

- Dosing and frequencies of medications in the above algorithms are recommendations. The recommended doses are not required for maintenance in the study and we anticipate that they may change given patient characteristics and variable response to medication, the rapidly evolving nature of acute pancreatitis, and hospitalist preferences. However, the mode of IV opioid administration (PDA vs PCA) should remain as assigned until transition to PO opioid.

- Each patient will be closely monitored for adverse events related to opioid administration to include cardiorespiratory decompensation, hemodynamic instability, nausea, vomiting, confusion, altered mental status, headache, drowsiness, etc. This monitoring will include continuous pulse oximetry in addition to vital sign measurement every 4 hours.

- The efficacy of each treatment arm to adequately control the patient's pain will be assessed with scheduled use of the Numeric Rating Scale (NRS) every 4 hours by the nursing staff. Pain rating on the NRS will be documented by the nursing staff after each assessment. In an NRS, patients are asked to circle the number between 0 and 10 that fits best to their pain intensity. Zero usually represents 'no pain at all' whereas 10 represents 'the worst pain ever possible'.

- Likert scale of 1 to 10 (1 = Very poor, 10= excellent) will be used to grade overall patient satisfaction with pain control.

- Once each patient's pain is well controlled on IV opioid administration (as determined by the attending physician) and they can tolerate intake by mouth, transition from IV to PO opioid medication can be made in each arm by the attending physician. If the patient is unable to tolerate either the PDA or the PCA arm for any reason and requires switching over to the other arm as part of his/her clinical care, they will be withdrawn from the study and their data will be excluded while analyzing the results. AP has a variable course and may require IV opioids

after transition to PO opioids. The modality of IV opioid administration will revert to the assigned treatment arm.

- Other aspects of each patient's routine clinical care will continue as per the attending physician under whom the patient is admitted regardless of treatment arm status (PDA vs PCA).
- At the end of their hospital stay, we will document the following outcomes:

1. <u>Primary outcome:</u> Length of stay (days)

2. <u>Secondary outcomes:</u>

a. Number of hours the patient is NPO before diet is initiated
b. Mean pain scores on NRS over the first 24 hours, second 24 hours and course of their hospital stay
c. Total opioid dose for pain control during hospitalization (average MME during hospital stay)
d. Time to transition to PO opioids
e. Opioid-related adverse events/side effects: respiratory decompensation, sleep-disordered breathing, hypotension, nausea, vomiting, constipation, drowsiness, confusion, delirium or other mental status changes, myoclonus, headache, urinary retention, physician suspected opioid abuse or any form of allergic reaction.
f. Use of naloxone and antiemetics
g. Number of rescue doses required daily and in total through the hospital stay
h. ICU transfer
i. 30-day readmission rates
j. All-cause inpatient mortality and opioid-related inpatient mortality
k. 30-day mortality
l. Daily MME on discharge

- We expect to enroll patients over a 36-month period from the start date of the study. Based on this, we expect patient enrollment to end by 4/30/2024. We will plan to perform data analysis at two points: 1. Interim data analysis at a predetermined point in the study (mid-point of study), and 2. At the end of the study once patient enrollment has been completed.

B. Statistical Considerations

a. ***Sample Size Justification:***

- Data from a retrospective study of acute pancreatitis patients receiving either patient-controlled analgesia (PCA, n=116) or conventional IV push (IVP, n=647) showed that mean length of stay was higher in the PCA group (9.9 ± 7.14 days) compared to the IVP group (6.4 ± 9.86 days). The effect size calculated using this data yielded a Cohen's d=0.42. Therefore, assuming a 5% error probability for two groups, the estimated sample size to achieve 80% statistical power was determined to be 87 patients per group. At the midpoint of the study when half of target sample size is reached, preliminary post-hoc analysis will be performed to determine effect size and statistical power.

b. ***Data Analysis:***

- Primary and secondary outcomes of interest will be studied as outlined above. Data will be presented as mean ± standard deviation, median [interquartile range; range], and count (percentage), as appropriate. Data will be graphed, QQ plots performed and Shapiro-Wilk test utilized to assess for normality. Statistical tests for primary and secondary outcome will be compared using independent samples t-test and Mann-Whitney U test, as appropriate. Categorical variables were investigated using Pearson's Chi-Square. Statistical significance will be assigned at 0.05. All data will be analyzed using the R statistical software.

C. Subject Selection

We will study 174 patients admitted within 24 hours to the hospital with AP between 18 and 65 years of age. Patients will be randomized to receive IV opioids either via PCA (n=87) or PDA (n=87). Exclusion criteria are as follows: known allergy or contraindication to opioids, active illicit drug use, chronic pancreatitis, pancreatic cancer, acute encephalopathy/psychiatric illness that would preclude ability to use PCA, chronic renal insufficiency with a Cr >2, acute renal insufficieny with a Cr >3, and known allergy to acetaminophen or hepatic dysfunction otherwise limiting acteaminophen use.

Inclusion criteria	Exclusion criteria
Diagnosis of AP confirmed by revised Atlanta criteria	Active illicit drug use
	Discharged from the ED
Admitted to the medical floor within 48 hours of ED arrival	Direct admission to ICU from ED
	Known allergy to opioid medications
Age 18-65	Age <18 or >65
	Known chronic pain syndrome or concurrent medical condition with chronic pain
	Active encephalopathy/confusion/delirium/psychiatric

	illness or any other condition that limits capacity
	Known chronic opioid use
	Renal insufficiency (baseline Creatinine of >2 and/or AKI with Cr>3 on admission)
	Known allergy to acetaminophen or hepatic dysfunction otherwise limiting acetaminophen use

Subjects will be enrolled without regard to race, gender, or vulnerable category status.

B4. POSSIBLE BENEFITS

Patients in this study will obtain no direct benefits from participation in the study. We hypothesize that based on prior studies in postsurgical patients, patients in the PCA arm may potentially have better control of their AP-related pain as compared to conventional physician directed analgesia. This may potentially result in higher patient satisfaction, early transition to oral analgesics, and shorter hospital stays. This information will be helpful in better management of the patients' pain with a PCA protocol in the future.

B5. POSSIBLE RISKS AND ANALYSIS OF RISK/BENEFIT RATIO

Patients enrolled in either arm of opioid administration are at risk of developing opioid-related adverse events. These range from minor gastrointestinal side effects such as nausea and vomiting to life-threatening cardiorespiratory decompensation and even death. However, pain control with opioids is the standard of care in treating pain associated with AP, and hence, our study does not impose any additional risk of opioid-related adverse events than what would be expected normally in these patients. However, we do acknowledge the risks associated with use of a PCA pump. Since opioid administration is controlled by the patient, there remains risk of delivering a higher opioid dose in a short duration of time, which may predispose the patient to potential acute opioid intoxication. However, our protocol has been designed to deliver lower individual doses of opioid with each dose when compared to PDA. Additionally, the patients will be closely monitored by vital sign measurement by the nursing staff as part of the usual care of AP patients, with availability of opioid reversal agents if needed

B6. RECRUITMENT AND CONSENT PROCEDURES

Recruitment

Patients will be identified as they are admitted to the hospital for management of AP. Our research staff will check with the admitting hospitalists/physicians on a daily basis for patients admitted with AP who may be eligible for enrollment in the study. Once we have identified a patient who meets the study criteria, our research staff will approach the patient and obtain informed consent.

Consent

After identifying a potentially eligible inpatient, a study Investigator will fully explain the purpose of this study to the patient. After fully answering the patient's questions and if the patient's consents to entering the study, a signed consent will be obtained. A study investigator will be responsible for obtaining written informed consent from each patient. The patient will be given a copy of the informed consent form, a copy will be placed in the patient's medical record and the original will be kept in the research files.

Subject Protection

We do not anticipate that any subjects would be vulnerable to coercion or undue influence. It will be made clear to the patients of the Principal and Co-Investigators that their participation is entirely voluntary and will not affect their clinical care with their physicians if they decline participation. Patients will also have the ability to discontinue their participation at any time.

B7. STUDY LOCATION

Privacy

All patient data will be kept in locked cabinets and rooms. All computer files containing patient information will be kept in a password-protected computer file.

Physical Setting

Informed consent and the collection of demographic data will be performed in the patient's room at the Beth Israel Deaconess Medical Center.

B8. DATA SECURITY

Research data will be stored on data-encrypted files on a secure server behind the BIDMC firewall. It will be password protected. Only research staff will have access to this data. Information from the questionnaires, medical history and contact information will be entered into a password protected Excel spreadsheet that is maintained by the principal investigator in a secure and encrypted location. Exported data will include only the necessary information and the least amount of personal identifiable data possible to complete analysis. Any exported data with identifiable information will be stored in password protected directory accessible only by study personnel. Finally, no identifiable information with be shared outside of BIDMC and all non-identifiable information will be pooled and released as a group

for the final study after statistical analysis is complete. Identifiers will be kept until completion of data analysis to allow for review of additional information that may become necessary during the statistical analysis phase. Patient MRN and unique study specific identifier will be kept until completion of data analysis or 1 year after study completion, whichever is greater. After this period, the file containing the patients' MRNs and study specific unique numerical identifiers will be deleted.

B9 Multi-Site Studies

Is the BIDMC the coordinating site? ☐ Yes ☐ No

Is the BIDMC PI the lead investigator of the multi-site study? ☐ Yes ☐ No

B10 Dissemination of Research Results

Patients will be thanked at time of enrollment, however research results will not be routinely distributed to the patients at completion of the study. If a patient specifically requests their individual results or the aggregated results, this will be permitted on an individual basis.