CLINICAL STUDY PROTOCOL

Title: Randomized Clinical Trial of IV Acetaminophen as an Adjuvant Analgesic to IV Hydromorphone for Treatment of Acute Severe Pain in Non-Elderly Emergency Department Patients

Sponsor

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Synopsis

Primary Objective

To compare the analgesic efficacy of IV acetaminophen as an analgesic adjunctive medication to IV hydromorphone for the treatment of acute pain in the ED.

Secondary Objectives (if applicable)

To compare the side effect profiles and adverse events associated with the combination of acetaminophen and hydromorphone vs. hydromorphone alone.

Primary Outcome Variables

The primary outcome is the between group difference in change in NRS pain scores from baseline (immediately before administration of analgesics) to 60 minutes post-baseline.

Secondary Outcome Variables (if applicable)

Secondary efficacy outcomes: difference in proportion of patients who choose to forego additional pain medication 60 minutes post-baseline when asked the question, "Do you want more pain medication?"; difference in proportion of patients who receive additional pain medication before 60 minutes post-baseline ("rescue" medication) and after 60 minutes. The incidence of adverse events and side effects in the two groups will be compared.

Study Duration

The study will continue until the enrollment target of 162 patients has been achieved. Based upon prior research studies, we anticipate that it will take approximately 5 months to reach our target.

Study Design
This is a double-blind, parallel group, randomized controlled trial comparing the analgesic efficacy of the combination of 1000 mg IV acetaminophen and 1 mg IV hydromorphone versus 1 mg IV hydromorphone alone for the treatment of acute pain in the Emergency Department.

Study Population
Adult patients (21 through 64 years of age) presenting to the Emergency Department with severe acute pain.

Number of Participants
Our target enrollment is 162 (81 in each arm).

Number of Study Sites
This study will be conducted in the Emergency Departments on the Moses and Einstein campuses of Montefiore Medical Center.

Visit Schedule Table (Optional)

Study Flow Chart (optional)

1 - Introduction
1.1 Introductory Statement

An estimated 44 million visits per year to US emergency departments (EDs) are associated with a painful condition.(1-2) Inadequate treatment of pain, has been demonstrated in many emergency departments.(3-6) Despite some progress, Todd's multicenter and multi-country study showed that only 50% of ED patients had at least a 2-point reduction of pain on a numeric rating scale (NRS) and 75% were discharged with moderate to severe pain.(7)

Intravenous acetaminophen is one drug that has been suggested to provide analgesic relief as good as or better than intravenous opioids in common acute painful conditions (e.g. renal colic, post-operative pain).(8-10) However, studies evaluating its use have been limited by small sample sizes and a range of methodologic limitations.(11)

Combination oral acetaminophen and oral opioids are commonly used in the ED. The rationale for combining different classes of analgesics is that the modes of action are different and may be at least additive if not synergistic. While this same rationale holds for combining intravenously administered acetaminophen and opioids, there have been no studies that examined the efficacy of this combination. Use of combination IV analgesics may provide enhanced analgesia and reduce the need for additional administration of opioid analgesics.

2 - Background
2.1 Background/prevalence of research topic

IV opioids have been the standard of care for moderate to severe pain in the ED. Recently non-opioid analgesics have been considered and tested for use in the ED as alternatives to IV opioid analgesics. The intravenous (IV) form of acetaminophen has been widely used in Europe for more than 20 years. The IV form obtained full FDA approval in the USA in 2010. A recent literature review revealed a total of 14 randomized controlled trials involving IV acetaminophen in the ED setting (11). Three of these (12-14), found a larger reduction in pain in the IV acetaminophen arm

than the IV opioid arm. All compared IV acetaminophen directly against another analgesic. The combination of acetaminophen and opioids in oral analgesics has been found repeatedly to be more efficacious than each alone. We reasoned that combining IV analgesics from these two classes might similarly improve the efficacy of treatment. We have not found any studies that examined IV acetaminophen as an adjunct to any IV opioid analgesic.

3 - Rationale/Significance

3.1 Problem Statement

Pain is a serious problem for many ED patients. Improving treatment is complicated by the increasing prevalence of opioid misuse and overdose in the outpatient setting, which has resulted in initiatives designed to reduce the administration and prescribing of oral opioids, and to substitute non-opioid medications (e.g. non-steroidal anti-inflammatories, acetaminophen) to the extent that such strategies are consistent with provision of satisfactory analgesia. Determining the optimal approach to acute pain management in the ED represents an important area of investigation.

3.2 Purpose of Study/Potential Impact

The purpose of the current study is to compare the analgesic efficacy of 1000 mg of acetaminophen combined with 1 mg hydromorphone to 1 mg of hydromorphone alone for the treatment of severe acute pain experienced by adult ED patients. If acetaminophen proves to be an efficacious adjunct to hydromorphone, care of ED patients in pain may be improved.

3.3 Potential Risks and Benefits

3.3.1 Potential Benefits

Determining whether IV acetaminophen is an efficacious adjunctive analgesic to IV hydromorphone will help the clinician choose effective therapies for the treatment of acute pain. Society will benefit from a greater understanding of the relative merits of opioid and non-opioid combination analgesia.

3.3.2 Potential Risks

It is likely that some subjects will experience adverse medication effects.

- All opioid pain medications such as **hydromorphone have side effects**, which include but are not limited to the following:
    - Common - not serious: nausea; vomiting; itching, drowsiness; flushing, dizziness, feeling light headed, drowsiness, constipation
    - Uncommon - serious: low blood pressure, low heart rate, slowed breathing, and decreased oxygen carried by your blood. This medicine can stop your breathing which can be fatal if not treated promptly.
- **IV acetaminophen**:
    - Common side effects: nausea, vomiting and headache.
    - Uncommon – not serious: itching, rash, constipation, stomach pain, pain at site of IV needle
    - Uncommon serious: none reported for short-term use

4 - Study Objectives

4.1 Hypothesis

IV hydromorphone in combination with IV acetaminophen will provide more efficacious pain relief compared to IV hydromorphone in combination with IV placebo (normal saline). The primary

outcome is the between group difference in change in NRS pain scores from baseline to 60 minutes post administration of study medications.

4.2 Primary Objective
To compare the analgesic efficacy of adding IV acetaminophen to IV hydromorphone for the treatment of acute pain in non-elderly ED patients.

4.3 Secondary Objectives (if applicable)
To compare the side effect profiles and adverse events associated with the combination of IV acetaminophen and IV hydromorphone and IV hydromorphone alone.

5 - Study Design
5.1 General Design
This is a double-blind, parallel group, randomized controlled trial comparing the efficacy and safety of 1000 mg IV acetaminophen combined with 1 mg IV hydromorphone vs. 1 mg IV hydromorphone plus placebo for the treatment of acute severe pain (defined as $\leq$ 7 days duration) in adult patients (age 21 through 64) presenting to the ED.

5.1.1 Study Duration (if applicable)
We anticipate achieving our target enrollment in approximately 5 months.

5.1.2 Number of Study Sites
This study will be conducted in the Emergency Departments on the Moses and Einstein campuses of Montefiore Medical Center.

5.2 Outcome Variables
5.2.1 Primary Outcome Variables
The primary outcome is the between group difference in change in numerical rating scale (NRS) pain scores from baseline to 60 minutes post administration of study medications. The NRS is a previously validated and reproducible measure of pain intensity ranging from 0 = no pain, to 10 = worst possible pain.

5.2.2 Secondary Outcome Variables (if applicable)
Difference in proportion of patients who choose to forego additional pain medication at 60 minutes post-baseline when asked the question, "Do you want more pain medication?"
Difference in proportion of patients who receive additional pain medication before 60 minutes post-baseline ("rescue" medication) and between 60 and 120 minutes post baseline. Difference in incidence of adverse events and side effects.

5.3 Study Population
Adult (ages 21 through 64 years of age) patients presenting to the ED with severe acute pain.

5.3.1 Number of Participants
148 patients are needed to detect a mean difference of 1.3 NRS units in the decrease of pain between the 2 treatment groups, a validated and reproducible effect size used in acute pain studies to indicate a minimally clinically significant difference(20-23), a within group standard deviation of 2.8 NRS units, significance level of 0.05, and 80% power. In order to ensure enrollment of a minimum of 148 patients with analyzable data, an additional 14 patients (~10%) will be enrolled. Thus the targeted sample size is 162 patients.

We used nQuery Advisor version 7.0 (Los Angeles, CA) to calculate the sample size.

5.3.2 Eligibility Criteria

Inclusion criteria

- Age 21 through 64 years of age: This is a study of adult ED patients.
- Pain with onset within 7 days of the ED visit: Pain within seven days is the definition of acute pain that has been used in the ED literature.
- ED attending physician's judgment that the patient's pain warrants IV opioids.
- ED attending physician's judgment that the patient has capacity to provide informed consent.
- Patients must be able to understand English or Spanish.

Exclusion criteria

- Use of opioids or tramadol within past 24 hours.
- Use of acetaminophen or non-steroidal anti-inflammatory medication within the previous 8 hours.
- Prior adverse reaction to opioids or acetaminophen.
- Chronic pain syndrome: frequently recurrent or daily pain for at least 3 months results in modulation of pain perception which is thought to be due to down-regulation of pain receptors. Examples of chronic pain syndromes include sickle cell anemia, osteoarthritis, fibromyalgia, and peripheral neuropathies.
- Medical condition that might affect metabolism or opioid analgesics or acetaminophen such as hepatitis, renal insufficiency or failure, hypo- or hyper-thyroidism, Addison's or Cushing's disease
- Pregnant or breastfeeding
- Alcohol intoxication: the presence of alcohol intoxication as judged by the treating physician may alter pain perception.
- Suspected chronic acetaminophen or opioid use, overdose., or suicidal ideation.
- SBP <100 mmHg: Opioids can produce peripheral vasodilation that may result in orthostatic hypotension.
- HR < 60/min: Opioids can cause bradycardia.
- Oxygen saturation < 95% on room air: For this study, oxygen saturation must be 95% or above on room air in order to be enrolled.
- Use of MAO inhibitors in past 30 days: MAO inhibitors have been reported to intensify the effects of at least one opioid drug causing anxiety, confusion and significant respiratory depression or coma.
- Patients using transdermal pain patches: pain patches may influence both the amount of pain patients report as well as the level of relief they obtain from other treatments.
- Taking any medication that might interact with one of the study medications, such as SSRI or tricyclic anti-depressants, benzodiazepine, buprenorphine, antipsychotics, anti-malarial medications (quinidine or halofantrine), amiodarone or dronedarone, diphenhydramine, celecoxib, ranitidine, cimetidine, ritanovir, terbinafine or St. John's Wort.
- Patients who have been previously enrolled in this same study: Patients may only be enrolled once.

6 - Methods

6.1 Treatment - Drug

6.1.1 Identity of Investigational Product/New Drug

Both acetaminophen IV (Ofirmev) and hydromorphone IV (Dilaudid) are FDA approved for clinical use.

6.1.2 Dosage, Admin, Schedule (if applicable)

- All patients will receive 1 mg IV hydromorphone.
- Acetaminophen + hydromorphone arm: In addition to the 1 mg IV hydromorphone patients will also receive 1000 mg IV acetaminophen in 100 ml normal saline over 5-10 minutes following randomization.
- Hydromorphone arm: In addition to the 1 mg IV hydromorphone patients will also receive 100 ml normal saline placebo over 5-10 minutes following randomization.

6.1.3 Method of Assignment/Randomization

An on-line program (www.randomization.com) will be used by the research pharmacist to generate the allocation schedule. Patients will be randomized in 27 blocks of 6.

6.1.4 Blinding and Procedures for Unblinding

Research subjects, clinicians, and research personnel will be blinded.

6.1.5 Packaging/Labelling

The pharmacist working in an area inaccessible to ED staff will ensure blinding by creating identical vials containing either 1000 mg acetaminophen in 100 ml normal saline or 100 ml normal saline placebo and numbering them sequentially for use in this study.

6.1.6 Storage Conditions

Study medications will be stored in the ED PYXIS at each site.

6.1.7 Concomitant therapy

Administration of concomitant medications will be at the discretion of the treating clinician and recorded. The administration of additional analgesics ("rescue" analgesia) will be recorded.

6.1.8 Restrictions

There are no relevant restrictions.

6.2 Assessments

6.2.1 Efficacy

Primary Outcome:

- The primary outcome is the between group difference in change in NRS pain scores from baseline to 60 minutes post administration of study medications.

Secondary Outcomes:

- Difference in proportion of patients who choose to forego additional pain medication at 60 minutes post-baseline when asked the question, "Do you want more pain medication?"
- Difference in proportion of patients who receive additional pain medication before 60 minutes and between 60 and 120 minutes post-baseline ("rescue" medication).
- Difference in proportion of patients who have one or more side effects in the 120 minutes..
- Incidence of adverse events.

6.2.2 Safety

- The Research Associate will remain at the patient's bedside for the first 5 minutes following the infusion of the medications.
- At 5, 15, 30, 45, 60, 75, 90, 105, and 120 minutes after the end of the infusion of the study medication, the RA will measure vital signs (including SaO2 by pulse oximeter), and record adverse events if they occurred.
- No further monitoring will be performed by the RA after 120 minutes.

6.2.2.1 Adverse Events Definition and Reporting

The RAs will ask patients questions about side effects of the medications that include incidence of nausea, vomiting, and pruritis. These are expected, usually minor adverse effects of the study medications. The RAs will monitor adverse events that include alterations in vital signs: oxygen desaturation below 95%, hypoventilation –respiratory rate per minute below 10, hypotension – systolic blood pressure below 90 mmHg, and bradycardia – heart rate below 50 beats per minute. Thresholds for the vital signs and protocolized response to values below the thresholds are described below.

- Vital signs (SaO2 obtained via pulse oximetry), pulse, respiratory rate, and blood pressure) will be monitored at baseline, 5, 15, 30, 45, 60, 75, 90, 105, and 120 minutes post-treatment. The RAs will remain at the bedside during the first 5 minutes after the infusion is completed in order to monitor for any adverse effects such as respiratory depression (RR<10) or oxygen desaturation (<95%).
- If the SO2 drops below 95% or the RR < 10 breaths per minute, a composite set of maneuvers will be performed:
  - The pulse oximeter will be confirmed to be properly placed on the patient's finger and be reading the patient's pulse, as determined by an appropriate waveform on the pulse oximeter.
  - The patient, if sleeping, will be gently shaken and verbally asked to take a few deep breaths.
  - The head of the gurney, if in the reclined position, will be raised.
- If any patient in either arm does not achieve an oxygen saturation of 95% or above despite these maneuvers, or if the oxygen saturation drops below 95% a second time, the patient will be placed on 2 liters nasal cannula oxygen and the ED attending will be notified immediately to determine what additional maneuvers are needed, including consideration of administration of 0.4 mg IV naloxone in repeated doses as necessary.
- If the HR is below 50 beats per minute the patient will be reassessed and the ED attending will determine what additional maneuvers are needed, including consideration of administration of 0.4 mg IV naloxone in repeated doses as necessary.
- If systolic BP is below 90 mmHg the patient will be reassessed, and a normal saline bolus will be administered if clinically indicated. The ED attending will then determine what additional maneuvers are needed, including consideration of administration of 0.4 mg IV naloxone in repeated doses as necessary.

All vital signs that fall below the thresholds described above will be reported to the Data Safety Monitoring (DSM) committee and included in the yearly progress report to the IRB. The DSM committee will be headed by Dr. David Esses, MD, the director of the Moses ED and include Dr. Andrew Chang, Director of Research Albany Medical Center. The committee will meet quarterly with the PI to 1) monitor adverse events and develop strategies to minimize these; and 2) monitor recruitment and enrollment.

6.2.3 Pharmacokinetics (if applicable)

Acetaminophen IV

- Half-Life: ~2.4 hours
- Onset of Action: 15 minutes (at conclusion of infusion)

- Peak Effect: ~1 hour
- Duration: ~6 hours

Hydromorphone IV

- Half-Life: ~2.3 hours
- Onset of Action: 10-15 minutes
- Peak Effect: 15-30 minutes
- Duration: 2-3 hours

6.2.4 Biomarkers (if applicable) - none

6.3 Study Procedures

- The RAs and attending physicians will identify eligible patients. The attending physician will assess the patient's capacity to consent.
- The RA and provider will describe the study to eligible patients and obtain patient consent. Both will document their participation with a note in Epic and by signing the consent document. This study in particular and research procedures in general are introduced during faculty meetings and reinforced with emails and Powerpoint presentations. The providers will be told that they will need to discuss the study with the patient, answer their questions, and sign consent document. The PI meets with providers in brief one-on-one sessions to describe the procedures.
- The RA will obtain a baseline pain score and baseline vital sign information.
- The healthcare provider will place an order in Epic for the study medication. The order will trigger a specific pocket in Pyxis to open. The research associate and the clinical nurse will then complete the RA/RN checklist (Appendix) to ensure verification, retrieval and administration of study medications. The RA will have the nurse remove the next study packet from the PYXIS, which will be a 100 ml vial containing either IV acetaminophen 1000 mg or IV normal saline. The contents will be concealed by the research pharmacist.
- All patients will receive 1 mg IV hydromorphone.
- After receiving hydromorphone, patients will receive the blinded study medication, which will either be 1000 mg IV acetaminophen in 100 ml or 100 ml normal saline placebo. This will be administered over 5-10 minutes.
- The RA will remain at the patient's bedside for the first 5 minutes following the infusion of the medications.
- At 5, 15, 30, 45, 60, 75, 90, 105, and 120 minutes following the completed infusion, the RA will obtain an NRS pain score, vital signs (including SaO2 by pulse oximeter), and record incidence of side effects and adverse events.
- At 60 minutes following infusion, the RA will also ask all patients if they want additional pain medication. The RA will inform the treating attending physician if the patient wants additional analgesia.
- The treating physician will be notified if the patient wants more analgesics. The patient and the treating physician will be told that the study has finished 120 minutes after end of infusion of study medication. No further monitoring will be performed by the RA after 120 minutes.
- The final diagnosis will be obtained from the chart and the treating attending physician at the time the patient leaves the ED.
- The RA will record all medications administered in the ED and the time of their administration from the chart and the treating attending physician.

6.3.1 Study Schedule

Patients will be enrolled during a single ED visit and study participation will conclude 120 minutes after infusion of study medication.

6.3.2 Informed Consent
All patients will be required to provide written informed consent prior to enrollment.

6.3.3 Screening
Screening, enrollment and data collection will be performed by trained, full-time, bilingual Research Associates (RAs) who staff the ED 24 hours per day in 8-hour shifts. All RAs have completed the University of Miami's Collaborative IRB Training Initiative Program for protection of human subjects in the social and behavioral track. We have had RAs collecting data in the emergency department for the past 10 years. They are completely familiar with conducting research in the ED setting and understand the ethical rationale and essential nature of obtaining informed consent. The PI will meet several times with the RAs before the protocol is initiated to review the informed consent process for this study and the data collection instrument to make sure that the RAs understand the study and can conduct it strictly according to protocol. Their training is described in detail in the Appendix.

The RAs will identify patients who are potentially eligible for the study in several ways. They will review the presenting complaint or triage description and consider all patients with complaint or mention of pain as potential participants. They will ask residents, nurses, physician assistants and attending physicians to refer potentially eligible patients for formal assessment of eligibility. The attending physician will be asked if they think a patient's pain warrants use of parenteral opioids and if the patient has capacity to provide informed consent.

6.3.4 Enrollment

6.3.5 Study visits
Subjects will be screened, consented and enrolled during their ED visit and will complete study participation two hours following infusion of study medication.

6.3.6 End of Study and Follow-up
Subject participation will conclude two hours after administration of study medication. No further follow-up is planned.

6.3.7 Removal of subjects
Subjects may withdraw from study participation at any time. Those who withdraw will receive "usual care" by the treating clinician.

6.4 Statistical Method
6.4.1 Statistical Design
The statistical design is parallel group design with patients randomly allocated to the two treatments.

6.4.2 Sample Size Considerations
A sample size of 148 (74 per group) was calculated based on the following parameters: alpha = 0.05, power = 0.8, between group delta 1.3 NRS units (commonly used in research as the minimum clinically significance difference or MCSD), and standard deviation of 2.8 NRS units (based on prior studies we have performed). We will enroll an additional 14 subjects (approximately 10%) in order

to account for potential protocol violations and missing data. Thus, our final sample size is 162 subjects.

We used nQuery Advisor version 7.0 (Los Angeles, CA) to calculate the sample size.

6.4.3 Planned Analyses

The planned analyses include: a comparison of the characteristics of the two treatment groups at baseline, the comparison of change in pain between baseline and 60 minutes post-baseline, comparison of proportion of patients who want additional analgesia at 60 minutes, comparison of the incidence of rescue medication, adverse events and side effects in the 120 minute period.

6.4.3.1 Primary Analyses

We will calculate the difference in NRS scores between baseline, immediately after the end of the infusion of the study medications (baseline) and 60 minutes for the 2 groups. An independent group t-test will be used to assess whether the mean change in NRS scores differ between the groups. If there are marked differences between the distributions of background characteristics a multi-variable regression will be performed to control for possible confounding. A difference of 1.3 NRS units or greater between change in pain in the two groups will be the criterion for a minimal clinically significant difference. This is based on several studies that have found this difference to be associated with the perception of change in pain, measured by labeling this degree of change in pain as “a little less” or “a little more pain.” (22)

6.4.3.2 Secondary Objectives Analyses

We will calculate the difference in the proportion of patients in each group who choose to forego additional pain medication at 60 minutes post-baseline based upon a simple dichotomous yes/no response to the patient-centered question, "Do you want more pain medication?" A chi-square test will be used to compare the proportions. We will also use chi-square tests to examine the proportion of rescue medication in the two groups. If there are marked differences between the distribution of background characteristics a multi-variable logistic regression will be performed to control for possible confounding.

6.4.3.3 Safety

Prior experience suggests that we will have insufficient power to detect differences in the incidence of adverse events unless the incidence is higher and the differences between groups are much larger than what we have observed in the past. Therefore we will report observed differences. Chi-square tests to assess whether the proportion of patients with one or more side effect differs between treatment groups. The individual side effects will be described in tables. If there are marked differences between the distributions of background characteristics a multi-variable logistic regression will be performed to control for possible confounding.

6.4.3.4 Analysis of Subject Characteristics

- Background characteristics: Age, sex, race/ethnicity, initial pain intensity, nausea and vomiting before administration of analgesics. Means and standard deviations, medians and interquartile ranges, and proportions will be used to describe the sample as appropriate.
- Cause, location of pain, and diagnosis: The etiology of pain will be described as trauma-related or not trauma-related. The location of pain will be described as: abdomen/pelvis, extremities, back,

head, chest, multiple locations, and other. The diagnosis will also be recorded. Frequencies will be presented.

- Anthropometrical measures: Patients will be asked to report their height and weight. Mean height and weight with standard deviations will be presented.

6.4.3.5 Interim Analysis (if applicable)

Dr. Andrew Chang will perform an interim analysis after half the sample is enrolled to consider stopping the trial if the analgesia provided by one treatment is found to be markedly superior to the other, or if the proportion of patients receiving rescue medication is substantially different between arms. We will use the Peto-Haybittle rule of requiring a p value of 0.001 or lower to indicate a difference between groups that would contribute to the decision to halt the trial.(24) (25) We calculated the size of the effect that would lead to rejection of the null hypothesis at this level of significance to assess whether it was clinically reasonable. A value that is thought of as a clinically important difference in pain between two treatment groups is 30 mm on a 100mm VAS for pain (equivalent to a 3 unit decrease on an NRS).(26) Thus, for example, a test of the difference between a 4.0 NRS unit decrease in pain in one group versus 1.0 NRS unit decrease in the other with a pooled SD of 2.8 would have a p value less than 0.001 with half the sample size. We do not plan to perform a test for futility. Finding that IV acetaminophen as an adjuvant medication to IV hydromorphone has similar efficacy as IV hydromorphone alone is an important finding that deserves to be disseminated. Given well documented publication bias against negative studies it is much more likely that this study will be published if we continue to collect the originally planned sample size. One could assume that both regimens are providing adequate analgesia based on numerous studies of this dose of IV hydromorphone.

All adverse events will be reported promptly to the DSMB as they occur and the decision to stop the trial based on the incidence and severity of the adverse events will be used to determine if the trial should be stopped early rather than on statistical grounds.

6.4.3.6 Health economic evaluation

Not applicable

6.4.3.7 Other

6.4.4 Subsets and Covariates

If there are serious imbalances in background characteristics multiple regressions will be run with those variables as covariates for the primary outcome. No subset analyses are planned.

6.4.5 Handling of Missing Data

Sensitivity analyses will be performed if there are missing primary outcome data.

7 - Trial Administration

7.1 Ethical Considerations

Patients will not receive any compensation for their participation in this study. All data collected will be maintained within locked file cabinets or within secure databases (i.e. REDCap).

7.2 Institutional Review Board (IRB) Review

Institutional Review Board review and approval will be obtained.

7.3 Subject Confidentiality

All data collection instruments will be secured within REDCap. The PI and co-investigators will be the only ones with access to the full database linking study IDs to patient identifying information.

7.4 Unanticipated Problems
Unanticipated adverse events will be reported promptly to the IRB.

7.5 Data Quality Assurance
The REDCap data collection instrument will be designed to identify out of range or abnormal values (e.g. age > 64, pulse rate of 5) and data quality reports will be run weekly.

7.5.1 Data Collection
All study data will be entered directly into REDCap by the Research Associates. Signed consent forms will be collected and kept under lock and key in a secure location.

7.5.1.1 Access to Source
The PI and co-investigators will be the only ones with access to the full database linking study IDs to patient identifying information.

7.5.1.2 Data Storage/Security
All data collection instruments will be secured within REDCap and will require a username and password for access. Hardcopy research records (i.e. written consents) will be kept under lock and key in the Department of Emergency Medicine at Montefiore Medical Center's Moses Division.

7.6 Study Records
Study records include all paper consents, IRB associated documents (application, protocol, certificate of translation, etc.) and the study data stored within REDCap.

7.6.1 Retention of Records
After the data analysis has been completed, data will be de-identified and stored on a secure, password protected server. Data will be kept in case of the future need for a meta-analysis of other studies that our department, or other investigators, have conducted or will conduct in the future.

7.7 Study Monitoring
Enrollment progress will be reviewed weekly.

7.8 Data Monitoring Plan
Data Safety Monitoring Committee: this committee will be headed by Dr. David Esses, Director of the Moses Division of the Department of Emergency Medicine, and include Dr. Andrew Chang, MD, Vice Chair for Research, Albany Medical Center. The committee will meet before data collection begins and quarterly with the PI to 1) monitor adverse events and develop strategies to minimize these; and 2) monitor recruitment and enrollment. The PI will analyze the data (fully blinded) to provide the DSMC with information on adverse events, recruitment and enrollment. Dr. Chang will conduct the interim analysis and the DSMC will review the results.

7.9 Study Modification
Any study modifications will be performed in compliance with existing IRB protocols.

7.10 Study Discontinuation

Study discontinuation prior to completion of target enrollment will be determined by the DSMC in compliance with existing IRB protocols.

7.11 Study Completion
Based upon prior studies, we anticipate achieving our target enrollment in approximately 5 months and will follow the standard IRB defined procedures for recording study milestones.

7.12 Funding Source
This study will be funded by the Department of Emergency Medicine

7.13 Publication Plan
Results of this investigation will be submitted for publication to a peer-reviewed journal in Emergency Medicine or Pain Management.

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APPENDIX

Research Associate Training

All data are collected by a team of research associates (RA). Research associates are required to have basic medical certifications, including the skills to assess vital signs and how to interact with people as patients. We also require them to be bilingual English and Spanish speakers because we believe it is essential that our research subjects represent our patient population. Prior to being hired, every research associate must prove their ability to speak Spanish fluently by having a conversation in Spanish with a departmental administrator, during which time we assess their ability to communicate with our patient population. After hiring, each research associate completes the required CITI coursework and then meets with each investigator one-on-one to discuss general themes of clinical research including research ethics, techniques of data collection, and pitfalls in data entry (incomplete data, missing data, and inaccurate data, such as race, which is particularly tricky in our patient population). Each new research associate then undergoes a two-month internship, during which time they shadow an experienced research associate, and learn the ins-and-outs of the job. Over these two months, the new research associate gradually takes on more and more responsibility under the tutelage of the seasoned research associate. At the end of the two-month period, each research associate has another in-person session with the investigators, during which time any questions are addressed.

Study specific training begins prior to IRB submission. The investigators discuss the study protocol and with the research associates, who are asked to provide their input. The research associates often comment on logistical issues of study flow. The research associates also provide feedback on the REDCap data collection instruments. Here too, they provide invaluable feedback on how to streamline these forms. Prior to initiation of the study, the investigator explains the study protocol and procedures to the RAs, typically using a Powerpoint presentation in groups of 1-3 research associates. These hour-long sessions are lively and interactive. Each research associates then performs mock enrollments using the investigators as subjects. These sessions too are full of lively give and take, during which adjustments in the data collection instruments can be made. During study enrollment, the investigators discuss the study and any questions that arise with each research associate on a near daily basis. We discuss any issues that occur in procedures that need intervention by the investigator such as pharmacy delays, nursing unavailability, or questions that the ED clinicians may have brought up. The investigators provide the research associates with feedback on data entry—such as when free texting was used rather than checkboxes, or when two different symptoms were lumped into one response category. The investigators remain in close contact with the RA throughout enrollment—each investigator typically receives a half dozen calls per week when questions of eligibility arise.

The research associates are trained by the PI or the Vice Chair of Research (Dr. Ben Friedman) in any changes that are made in procedures.

Checklist for verification, retrieval and administration of study medications

Patient's Name:

Patient's MRN:

Place patient ID label here

Study Protocol Name:
_____

Study Protocol Number: _____

Research Associate: Complete prior to drug removal

I have verified the following:

- ☐ Patient meets inclusion criteria
- ☐ Patient is not allergic to the drug
- ☐ Patient does not have any exclusions
- ☐ Consent is signed

RA Signature: _____Date_____ Time_____

Medication verification at Pyxis: Two person (RA and Nurse) checks:

- ☐ Nurse reads aloud the physician order from Epic including drug name, dose, route and study number while RA confirms it agrees with the consent
- ☐ RA reads aloud from the consent the study drug name and study number while the Nurse confirms it agrees with the Pyxis screen
- ☐ A patient label and the drug label from the study medication are placed on the medication to be administered to the patient

Verification at the Bedside: two person (RA and Nurse) checks:

- ☐ Nurse and RA go to the patient and confirm the patient's agreement to participate in the study and that the consent has been signed
- ☐ RA obtains vital signs, shares with Nurse and documents them in Red Cap
- ☐ Nurse verifies the *dual identifiers* against the patient label to confirm that it is indeed the correct patient

Nurse signature: _____ Date_____ Time _____

RA signature:___
Date_____Time_____

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