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Title: Randomized clinical trial of IV acetaminophen as an adjunctive analgesic to IV hydromorphone

Introduction and Background: An estimated 44 million visits per year to US emergency departments (EDs) is due to pain (Pletcher 2008; Nawar 2007). Oligoanalgesia, or the inadequate treatment of pain, has been a vexing problem in emergency departments (Wilson 1989, Rupp 2004, Ritsema 2007, Stalnikowicz 2005). Despite some progress, Todd's recent multicenter and multicountry 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 (Todd, 2007). Elderly patients are at even more risk for undertreatment of pain.

Acetaminophen has been a mainstay for pain treatment and fever control. The intravenous (IV) form has been widely used in Europe for more than 20 years. The IV form obtained full FDA approval in the USA in 2010. A literature review reveals a total of 14 randomized controlled trials involving IV acetaminophen in the ED setting (Masoumi 2014, Shams 2014, Grissa 2011, Serinken 2012, Zare 2014, Eken 2014, Bektas 2009, Craig 2012, Morteza-Bagi 2015, Turkcuer 2014, Pickering 2015, Azizkhani 2013, Oguzturk 2012, Aksel 2015). Three of these (Masoumi 2014, Shams 2014, Grissa 2011) showing a significant reduction in pain. However, only one included elderly patients (Azizkhani 2013) and all compared IV acetaminophen directly against another analgesic. In addition, the majority of the trials had significant methodological flaws making their conclusions suspect.

For this study, we wish to examine the analgesic efficacy of IV acetaminophen as an *adjunct* to IV hydromorphone in the treatment of acute severe pain in elderly ED patients.

Primary 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.

Secondary hypotheses: There will be a 10% or more difference in the proportion of patients who choose to forgo additional pain medication when asked at 60 minutes. There will be a greater decrease in NRS pain scores at various other time points for the IV hydromorphone + IV acetaminophen group compared to the IV hydromorphone + placebo group.

Study design: Randomized controlled trial

Randomization: An on-line program (www.randomization.com) will be used to generate the allocation schedule.

Subjects: The target population is 162 elderly (aged 65 years and above) ED presenting to the emergency department with acute severe pain.

Trained, full-time, bilingual research associates (RAs) 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. Many of the RAs have collected data for our studies over many 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.

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 also ask residents, nurses, physician assistants and attending physicians if they feel a patient's pain warrants use of parenteral opioids. They will then assess whether the patient meets the inclusion criteria. If the patient meets the criteria, the RA will describe the study, review the informed consent document with the patient, and obtain the patient's written consent. Only patients can consent for themselves. The RAs are all fluent in Spanish.

A. Inclusion criteria

1. Age greater than 65 years: This is a study of elderly ED patients.

2. Pain with onset within 7 days: Pain within seven days is the definition of acute pain that has been used in ED literature.

3. ED attending physician's judgment that patient's pain warrants IV opioids: The factors that influence the decision to use parenteral opioids are complex. An approach that is commonly taken to address the issue of patient selection in drug trials is to use a specific condition (e.g., renal colic) that would generally be thought to be appropriately treated with an opioid analgesic, thereby eliminating individual judgment about eligibility for the study. However in order to maximize the external validity of the role of opioids in the ED setting, we decided to enroll patients with a variety of diagnoses, all with a complaint of acute pain.Opioids are not an appropriate treatment for all patients who present with a complaint of pain (e.g., gastroenteritis, migraine). Therefore, unless there is a restriction to patients with a specific diagnosis, either an extensive list of diagnoses and situations in which opioids are indicated must be specified, or clinical judgment needs to be used. We have opted for the latter, since it most closely approximates the circumstances of clinical practice.

B. Exclusion criteria

1. Use of other opioids or tramadol within past 24 hours: to avoid introducing assembly bias related to recent opioid use, since this may affect baseline levels of pain and need for analgesics.

2. Prior adverse reaction to hydromorphone, morphine, or acetaminophen.

3. 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.

4. Alcohol intoxication: the presence of alcohol intoxication as judged by the treating physician may alter pain perception.

5. SBP <100 mm Hg: Opioids can produce peripheral vasodilation that may result in orthostatic hypotension.

6. HR < 60/min: Opioids can cause bradycardia.

7. Oxygen saturation < 95% on room air: For this study, oxygen saturation must be 95% or above on room air in order to be enrolled.

8. 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.

9. $C0_2$ measurement greater than 46: In accordance with standard protocol, three subsets of patients will have their CO_2 measured using a handheld capnometer prior to enrollment in the study. If the CO_2 measurement is greater than 46 then the patient will be excluded from the study. The 3 subsets are as follows:

    a. All patients who have a history of COPD
    b. All patients who report a history of asthma together with greater than a 20 pack-year smoking history
    c. All patients reporting less than a 20 pack-year smoking history who are having an asthma exacerbation

10. 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.

11. Patients who have been previously enrolled in this same study: Patients may only be enrolled once.

Measures

A. Outcomes:

1. Primary outcomes
    a. The primary outcome is the between group difference in change in NRS pain scores from baseline to 60 minutes post administration of study medications.
2. Secondary efficacy outcomes
    a. Difference in proportion of patients who choose to forgo additional pain medication at 60 minutes post-baseline when asked the question, "Do you want more pain medication?"
    b. Difference in change in NRS pain scores between the 2 groups at multiple time points (5, 15, 30, and 45 minutes).
    c. Patient Satisfaction: at the end of the study, both groups will be asked the question, "If you had acute pain again, would you want the same protocol?"
    d. Pain Relief Scale: Response to treatment will also be assessed by a 5-point ordinal pain relief scale with the following categories: 0 no relief, 1 a little relief, 2 some relief, 3 a lot of relief, 4 complete relief. This scale has been used extensively in research in acute and chronic pain. The verbal descriptors of pain relief make it easy for patients to use, as they are terms used in day-to-day speech.
    e. Difference between the 2 groups in incidence of hypoventilation (RR < 10 /min), oxygen desaturation (O2 saturation < 92%), hypotension (SBP < 90 mmHg), bradycardia (HR < 50/min), nausea, vomiting, pruritus, and drowsiness.

B. Descriptive Variables:

1. Background characteristics: Age, sex, race/ethnicity, marital status, education, current work status and type of insurance (no insurance, private insurance, Medicaid, Medicare, other). This information will be used to describe the sample.

2. 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.

3. Anthropometrical measures: Patients will be asked to report their height and weight.

Study Procedures:

1. The RA will describe the study to eligible patients and obtain patient consent.
2. The RA will obtain a baseline pain score and baseline vital sign information.
3. 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 1 gm (100 ml) or 100 ml normal saline placebo. These will be blinded by the research pharmacist.

4. All patients will receive 0.5 mg IV hydromorphone
5. All patients will receive the blinded study medication, which will either be 100 ml IV acetaminophen or 100 ml normal saline placebo. This will be administered over 5-10 minutes.
6. The RA will remain at the patient's bedside for the first 5 minutes following the infusion of the medications .
7. At 5 minutes, the RA will obtain an NRS pain score, a categorical pain relief descriptor, vitals signs, and assess for adverse events.
8. At 15 minutes, the RA will obtain an NRS pain score, a categorical pain relief descriptor, vital signs, and assess for adverse events.
9. At time 30 and 45 minutes, the RA will obtain an NRS pain score, a categorical pain relief descriptor, vital signs (including SO_2 by pulse oximeter), and assess for adverse events.
10. At 60 minutes (the study's primary hypothesis endpoint) the RA will ask all patients their NRs pain score, a categorical pain relief descriptor, and also ask if they want additional pain medication. The RA will then immediately inform the treating attending physician that the patient does or does not want additional analgesia. Subsequent care will be at the discretion of that physician. The RA will also obtain vital signs (including SO_2 by pulse oximeter), and assess for adverse events.
11. The final diagnosis will be obtained from the chart and the treating attending physician at the time the patient leaves the ED.
12. The RA will obtain and record all medications administered in the ED and the time of their administration from the chart and the treating attending physician.

Safety monitoring

Data Safety Monitoring committee: this committee will be headed by Dr. Polly Bijur, PhD, an epidemiologist, and include Dr. David Esses, MD, the director of the Moses ED. The committee will meet every month with the PI to 1) monitor adverse events and develop strategies to minimize these; and 2) monitor recruitment and enrollment.

Adverse events will include incidence of oxygen desaturation below 95%, hypoventilation, hypotension, and bradycardia. Thresholds for the vital signs and protocolized response to values below the thresholds are described below.

1. Vital signs (SO_2 obtained via pulse oximetry), pulse, respiratory rate, and blood pressure) will be monitored at baseline, 5 minutes, 15 minutes, 30 minutes, 45 minutes, and 60 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%).
2. If the SO_2 drops below 95% or the RR < 10 breaths per minute, a composite set of maneuvers will be performed:
    a. 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.
    b. The patient, if sleeping, will be gently shaken and verbally asked to take a few deep breaths.
    c. The head of the gurney, if in the reclined position, will be raised.
3. 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.
4. If the HR <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.
5. If systolic BP< 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.

Data Management and Analysis: We will use SPSS 17.0 for Windows (SPSS, Inc., ChicagoIL) for statistical analysis

1. Sample size calculation: 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 wish to enroll an additional 14 subjects (approximately 10%) in order to account for potential protocol violations and missing data. Thus, our final proposed sample size is 162 subjects.

2. Data Processing: During the data collection period, data will be entered directly into REDCap.

3. Analysis: Descriptive data will be calculated for all variables. The characteristics of patients in the two groups will be compared in order to confirm adequacy of randomization. If there is unequal distribution of background variables with p values of 0.15 or less, we will include them in a multivariate analysis of the outcomes. We will

calculate the difference in NRS scores between baseline (time zero) and 60 minutes for the 2 groups. We will also calculate this difference at other time points as well. We will calculate the difference in the proportion of patients in each group who choose to forgo 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?" We will also examine the distribution of satisfaction and relief scores, and the incidence of adverse events. Chi-square tests will be used to compare the distribution of the categorical variables between groups and t-tests will be used to compare means. Ordinary least squares multiple regression will be used to compare change in mean NRS with selected covariates, and logistic regression will be used to test the difference between dichotomous variables while controlling for any baseline characteristics that may have been maldistributed in the randomization by chance. The relief and satisfaction Likert scales will be dichotomized for these analyses before examining their association with group assignment. We will use 95% confidence intervals to compare means, proportions, and differences in both whenever possible. Otherwise, we will use a standard significance criterion of $p<0.05$.

4. Computer data security, subject confidentiality, data storage, and maintenance: All data collection instruments will be secured within REDCap. Research records will be kept under lock and key in the Department of Emergency Medicine at Montefiore Medical Center's Moses Division. Electronic database will require a username and password. The PI and co-investigators will be the only ones with access to the full database linking study IDs to patient identifying information. The limited electronic database used for analysis will be in the possession of the PI and be password protected. After the data analysis has been completed, data will be de-identified and stored on a secure, password protected computer. Data will be kept in case of the future need for a meta-analysis of other studies that our department has conducted or will conduct in the future.

References

1. Nawar EW, Niska RW, Xu J. National Hospital Ambulatory Medical Care Survey: 2005 emergency department summary. Adv Data 2007:1-32.

2. Pletcher MJ, Kertesz SG, Kohn MA, et al. Trends in opioid prescribing by race/ethnicity for patients seeking care in US emergency Departments. JAMA 2008;299:70-8.

3. Ritsema TS, Kelen GD, Pronovost PJ, et al. The national trend in quality of emergency department pain management for long bone fractures. AcadEmerg Med 2007;14:163-9.

4. Rupp T, Delaney KA. Inadequate analgesia in emergency medicine. Ann Emerg Med 2004;43:494-503.

5. Stalnikowicz R, Mahamid R, Kaspi S, et al. Undertreatment of acute pain in the emergency department: a challenge. Int J Qual Health Care 2005;17:173-6.

6. Todd KH, Ducharme J, Choiniere M, et al. Pain in the emergency department: results of the pain and emergency medicine initiative (PEMI) multicenter study. J Pain 2007;8:460-6.

7. Wilson JE, Pendleton JM. Oligoanalgesia in the emergency department. Am J Emerg Med 1989;7:620-623.

8. MasoumiK,ForouzanA,AsgariDarianAetal.Comparisonofclinicalefficacyofintravenousacetaminophenwithintravenousmorphineinacuterenalcolic:arandomized,double-blind,controlledtrial.EmergMedInt2014;2014:571326.

9. ShamsVahdatiS,MortezaBaghiHR,GhobadiJetal.Comparisonofparacetamol(Apotel®)and morphineinreducingpostpureheadtraumaheadache.AnesthPainMed2014;21:e14903

10. GrissaMH,ClaessensYE,BouidaWetal.Paracetamolvspiroxicamtorelievepaininrenalcolic. Resultsofarandomizedcontrolledtrial.AmJEmergMed2011;29:203-6.

11. SerinkenM,EkenC,TurkcuerIetal.Intravenousparacetamolversusmorphineforrenalcolicinth eemergencydepartment:arandomizeddouble-blindcontrolledtrial.EmergMedJ2012;29:902-5.

12. ZareMA,GhalyaieAH,FathiMetal.Oraloxycodoneplusintravenousacetaminophenversusintr avenousmorphinesulfateinacutebonefracturepaincontrol:adouble-blindplacebo-controlledrandomizedclinicaltrial.EurJOrthopSurgTraumatol2014;24:1305-9.

13. EkenC,SerinkenM,ElicabukHetal.Intravenousparacetamolversusdexketoprofenversusmorp hineinacutemechanicallowbackpainintheemergencydepartment:arandomizeddouble-blindcontrolledtrial.EmergMedJ2014;31:177-81.

14. BektasF,EkenC,KaradenizOetal.Intravenousparacetamolormorphineforthetreatmentofrenalcolic:arandomized,placebo-controlledtrial.AnnEmergMed2009;54:568-74.

15. CraigM,JeavonsR,ProbertJetal.Randomisedcomparisonofintravenousparacetamolandintravenousmorphineforacutetraumaticlimbpainintheemergencydepartment.EmergMedJ2012;29:37-9.

16. Morteza-BagiHR,AmjadiM,Mirzaii-SousefidiRetal.ThecomparisonofApotelpluslowdosemorphineandfulldoseofmorphineinpainreliefinpatientswithacuterenalcolic.AddictHealth2015;7:66-73.

17. TurkcuerI,SerinkenM,EkenCetal.Intravenousparacetamolversusdexketoprofeninacutemigraineattackintheemergencydepartment:arandomizedclinicaltrial.EmergMedJ2014;31:182-5

18. PickeringG,MoustafaF,MacianNetal.Anewtransmucous-buccalformulationofacetaminophenforacutetraumaticpain:anon-inferiority,randomized,double-blind,clinicaltrial.PainPhysician2015;18:249-57.

19. AzizkhaniR,PourafzaliSM,BaloochestaniEetal.Comparingtheanalgesiceffectofintravenousacetaminophenandmorphineonpatientswithrenalcolicpainreferringtotheemergencydepartment:arandomizedcontrolledtrial.JResMedSci2013;18:772-6.

20. OguzturkJ,OzgurD,TurtayMGetal.Tramadolorparacetamoldonoteffectthediagnosticaccuracyofacuteabdominalpainwithsignificantpainrelief-aprospective,randomized,placebocontrolleddoubleblindstudy.EurRevMedPharmacolSci2012;16:1983-8.

21. AkselG,GülerS,DoğanNÖetal.Arandomizedtrialcomparingintravenousparacetamol,topicallidocaine,andiceapplicationfortreatmentofpainassociatedwithscorpionstings.Hum ExpToxicol2015;34:662-7.