

Parenteral Acetaminophen for Treatment of Generalized Headache Presentations in the Emergency Department

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Introduction

Headaches represent over 3 million Emergency Department (ED) visits per year comprising 2.4 percent of all ED visits¹⁰, and are thought to be one of the three most common complaints of patient presentations to EDs across the country. The most prevalent group presenting to Emergency Departments across the U.S. range in ages between 18-44 with 1626 visits per 100,000¹⁰. Expenditures totaling over \$408 million were reported as of 2008 in terms of hospitalization costs¹¹. Treatment of headache presentations in the acute setting remains complex, often requiring an individualized regimen that is patient-tailored. There are many proposed methods and clinical guidelines of treating acute headache presentations however data on intravenous acetaminophen usage in these settings is lacking^{11,12}. Intravenous acetaminophen in the post-operative period has been found by retrospective medical use evaluation (MUE) surveys to reveal significant success at sparing narcotics as a part of a multi-modal approach to analgesia²³. It has also displayed effectiveness in the setting of treatment of acute renal colic when compared to morphine directly³³. While current recommendations for acute headache treatment do not routinely include opiates, many patients regularly use or require some form of opiate analgesia, complicating current approaches. Assessing the usage of intravenous acetaminophen in the setting of acute headache as an adjunct to standard therapy as part of a multi-modal approach may display increased efficacy in terms of pain reduction and purported narcotic-sparing effects.

Aims

1. A randomized, double-blind, placebo-controlled trial investigating the clinical efficacy of IV acetaminophen as an adjunct to a standard therapy for the treatment of patients who present to the emergency department with a chief complaint of "headache" or variants thereof. Protocols included administration of prochlorperazine, diphenhydramine, 1000ml 0.9% normal saline IV bolus, and randomization to receive either 1,000mg parenteral acetaminophen (1000mg/100ml) or 100ml of 0.9% normal saline as control in the placebo group.
2. Independent of the clinician's ultimate disposition of the patient, data collection was performed to ascertain three primary outcome measurements:
 - 1) The presumed efficacy of parenteral acetaminophen as an adjunct treatment for headache in addition to a standard therapy. The primary end-point was reduction in visual analog scale pain scores on a 1-10 level at 90 minutes.
 - 2) Decreased requirement of "rescue" pain medicines (with particular interest to narcotic sparing) during ED visit
 - 3) Decreased time to disposition

Hypothesis:

Parenteral acetaminophen will provide measurable analgesic effect for treatment of headaches. Presumptively, patients will require less "rescue" medications after initial treatment with the IV acetaminophen therapy and have notable results in terms of pain score reduction. Additionally, previous clinical trials in postoperative pain management have revealed a narcotic sparing effect of IV acetaminophen. This study could demonstrate such an effect for the treatment of cephalgia. Anticipated effects of the drug's properties and bioavailability are presumed to provide adequate analgesia which will additionally result in a shortened clinical course.

Methods:Protocol

Patients presenting with chief complaint of headache or variant thereof were provided informed consent. After initial assessment of the patient by the provider including review of exclusion criteria, an order set was utilized in the electronic medical record to select a pre-selected order cluster including prochlorperazine 10mg IV bolus, diphenhydramine 25mg IV bolus, 1000ml 0.9% normal saline bolus, and "study drug". The "study drug" was either 100ml 0.9% sodium chloride in a minibag, or 1000mg IV acetaminophen transferred from the manufacturer's vial into a 100cc minibag. All patients received both prochlorperazine, diphenhydramine, and 1000ml 0.9% normal saline immediately and then subsequently the 'study drug'. This was sent from Pharmacy via tube system to ensure blinding. Both IV acetaminophen and placebo were administered via IV infusion over a 15 minute interval as is required by the manufacturers dosing administration instructions. The study was designed to be double blinded to both physician and patient, therefore patients were randomized by the pharmacist to either treatment arm "A" or "B", where "A" represented acetaminophen, and "B" represented placebo. The pharmacists used a numeric identifier in a logbook to track whether patients received the study drug or placebo. The study blinding was able to be broken at any time by the ED physician if necessary.

Patient assessment:

ED staff in the Emergency Department completed a stratification form that noted the patient age, chief complaint, and pain assessment intervals at time of arrival, time of "study drug" administration, reassessment at 30 minute intervals thereafter, and additional reassessment if a "rescue" medication was later used. A standardized Visual Assessment Scoring scale was utilized on a scale of increasing pain intensity from 1-10. The screening form was also used to delineate which patients met inclusion or exclusion criteria. The treating ED physician discussed the study in detail with the patient and obtained informed consent for enrollment

Adverse events:

In the event of adverse reaction to the IV infusion of the "study drug", the infusion would be stopped and pharmacy contacted if required to "break" the double blinding to determine which medication was administered. During the study, no requirements for cessation of infusions were noted. Any and all methods to treat the patient for an adverse drug reaction were available using current clinical standard of care.

Inclusion/Exclusion criteria:

Inclusion criteria:

- 1) Any patient presenting with chief complaint of headache, migraine headache, tension headache, cluster headache or headache not otherwise specified
- 2) Adults age 18 – 65 years
- 3) Reporting pain as >4 using 10-point visual analog scale

Exclusion criteria

- 1) Age < 18 years
- 2) Age > 65 years
- 3) Total cumulative dose of acetaminophen >2600mg within past 24 hours.
- 4) Physical or mental disability hindering adequate response to assessment of pain
- 5) Mental disability limiting ability to give consent
- 6) Hemodynamic instability or medical condition requiring acute lifesaving intervention
- 7) Documented or suspected pregnancy or active breastfeeding
- 8) Any known contraindication to acetaminophen use such as liver failure, cirrhosis, hypersensitivity, allergic reactions, etc.
- 9) Any contraindication or reported allergy to the use of prochlorperazine and/or diphenhydramine

Results

An estimated 100 patients were needed for the study to have an 80% power to detect a difference at an alpha of 5%. 100 patients were enrolled in the study in total utilizing convenience sampling methods. 4 enrolled patients were excluded from data analysis secondary to age cutoff, 2 patients were excluded secondary to repeat enrollment (only the initial enrollment was factored into consideration) and 3 patients excluded secondary to insufficient data recording by either physician, ancillary staff or EHR reporting. Excluded additionally in the study was 1 patient who was found to have a brain mass possibly noted as a glioma. 45 patients were administered placebo and 45 administered IV acetaminophen. Both groups received diphenhydramine, prochlorperazine, and 1L 0.9% NS bolus. At no time was the study blinding required to be broken secondary to patient decompensation or deleterious effects.

Of the 90 patients sampled in the study, 51% reported their race as Black or African American, 47% as White, Hispanic or Caucasian, 1% as American Indian or Alaskan Native (fig1). No patients reported race of Eastern Indian, Western Indian or Asian or Pacific Islander.

Demographics

Black or African American	46
White, Hispanic, or Caucasian	43
Asian/Pacific Islander	0
American Indian or Alaskan Native	1

Figure 1. Individual Race as per hospital federal reporting regulations.

A significantly higher portion of women (n=70) when compared to men (n=20) were noted as participants in the study. The mean age of participants was 31 in males and 38 in females. Age groups of study participants were further divided with notable findings of the majority of males being within ages 18-29, and females being ages 30-39 (fig 2).

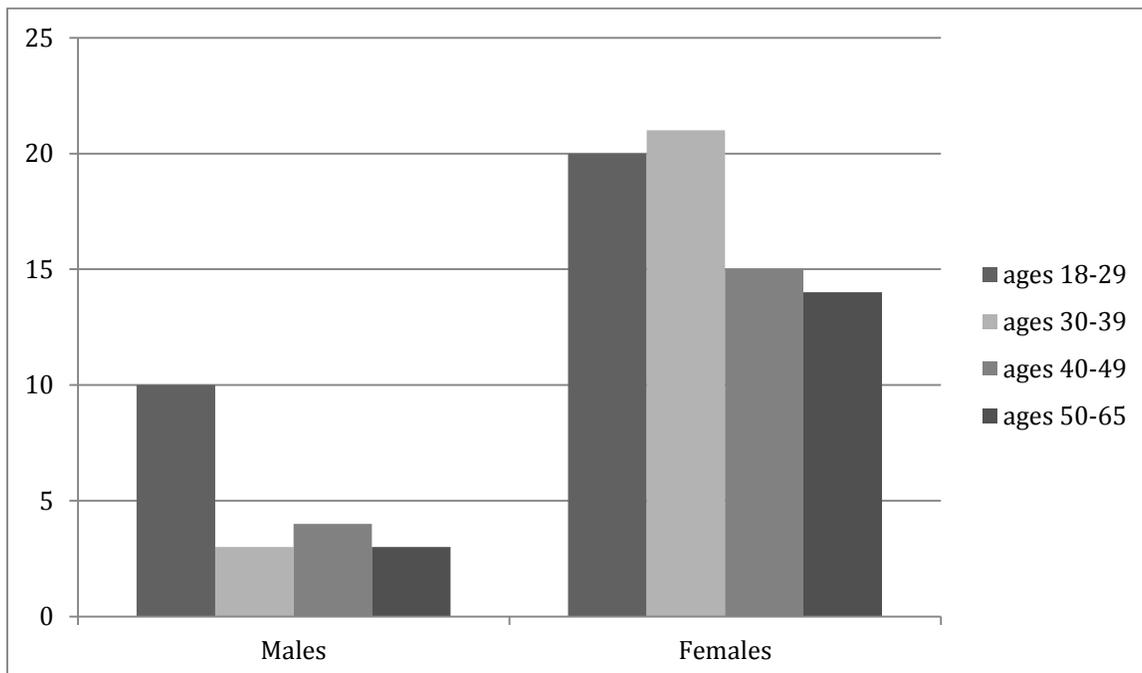


Figure 2. Demographics in age range categories

Pain scores were analyzed at 0, 30, 60, and 90 minutes after study drug administration. Pain scores were reported on a 1-10 scale based on current Visual Analog Scale guidelines. Of the (n=45) patients who received IV acetaminophen, 36 reported a statistically significant decrease by pain score reporting of ≥ 2 from presentation at the 90 minute mark. Nine patients reported pain scores which were unchanged from initial presentation, increased, or decreased by <2 at the 90 minute assessment. Of the (n=45) patients who received placebo, 25 reported a statistically significant decrease by pain score reporting of ≥ 2 from presentation at the 90 minute mark. 20 patients reported pain scores which were either increased, unchanged from initial presentation, or decreased by <2 at the 90 minute assessment. ($P < 0.01$, CI $> 95\%$). (Fig.3).

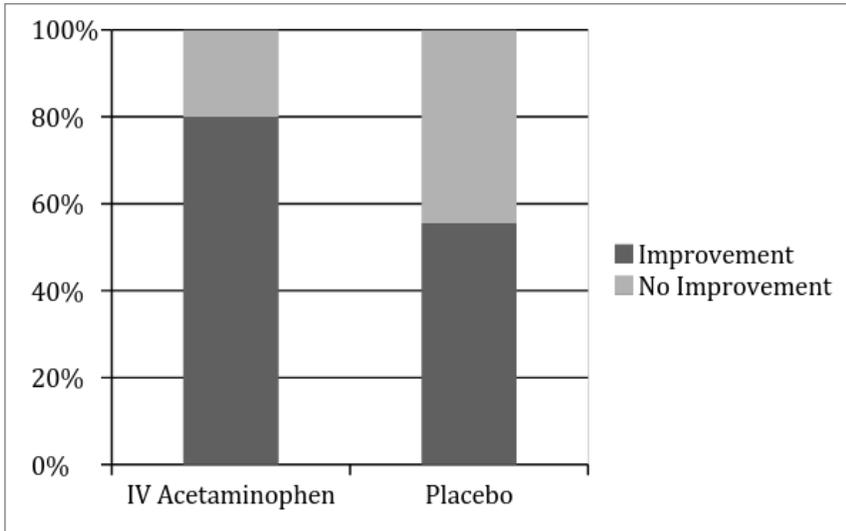


Figure 3. Improvement of VAS pain score reporting ≥ 2 from presentation at the 90 minute mark

41 patients required some form of 'rescue' medication in addition to the initially administered medications. 17/45 (38%) of patients who received IV acetaminophen required rescue analgesia, opposed to 24/45 (53%) of patients in the placebo group. ($p 0.13$, CI > 90) (Fig 4,6) .

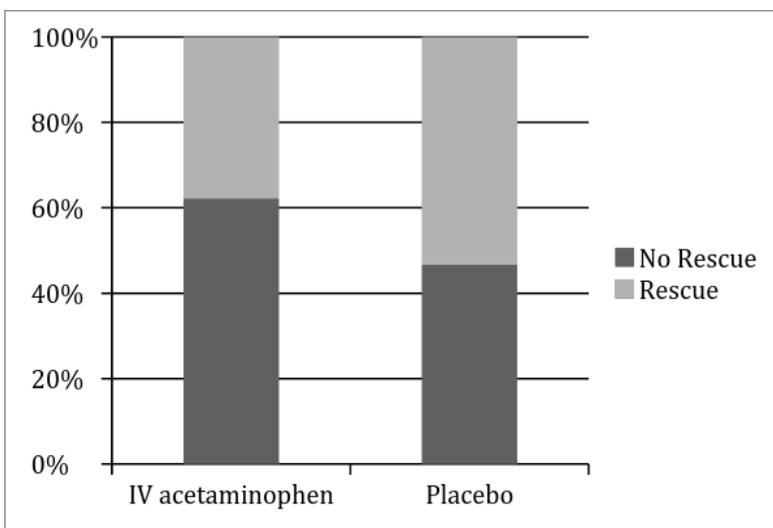


Figure 4. Comparative percentages of those requiring rescue analgesia in both IV acetaminophen and Placebo

Seventeen out of the 41 patients who required rescue analgesia received NSAIDs (IV ketorolac in all instances) as part of the rescue regimen, 8 in the IV acetaminophen treatment arm and 9 in the placebo arm. Nine patients received narcotics as part of a rescue formulation, 4 in the IV acetaminophen treatment arm, and 5 in the placebo arm. The narcotics administered included hydrocodone, hydromorphone, meperidine, and fentanyl. Some patients received combination rescue medications including narcotics and NSAIDs alone, in combination or in addition to other medications including orphenadrine, triptans, and steroids depending on clinician discretion (fig 5).

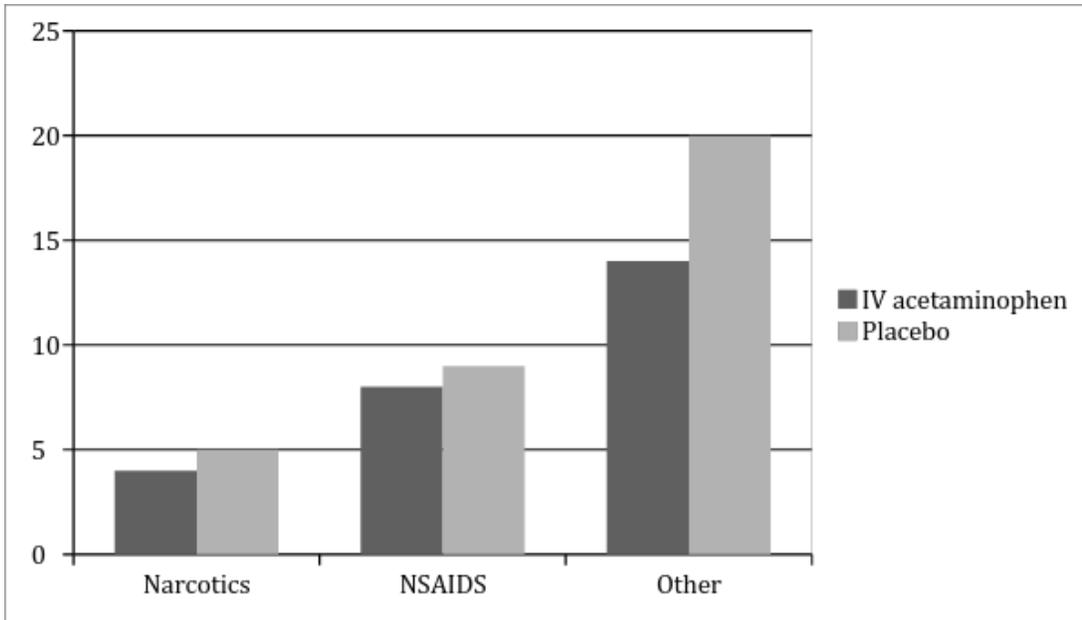


Figure 5. Numeric comparison of rescue analgesics for both IV acetaminophen and placebo arms.

Mean time to two point decrease in pain score was 49.2 minutes post administration of IV acetaminophen, prochlorperazine and diphenhydramine. Mean time of statistically significant score decrease was 71.3 minutes post administration of IV 0.9% NS, prochlorperazine and diphenhydramine.

Mean pain intensity scoring (VAS) was noted for both groups. For the acetaminophen arm the initial mean pain score was 8.67, for the placebo arm 8.61. At 30 minutes 6.61 for Acetaminophen, 7.14 for placebo. At 60 minutes 4.41 for Acetaminophen, 5.12 for placebo. At 90 minutes 2.23 for Acetaminophen, 3.99 for placebo. ($P < 0.01$, $> 99\%$ CI). (Fig 6)

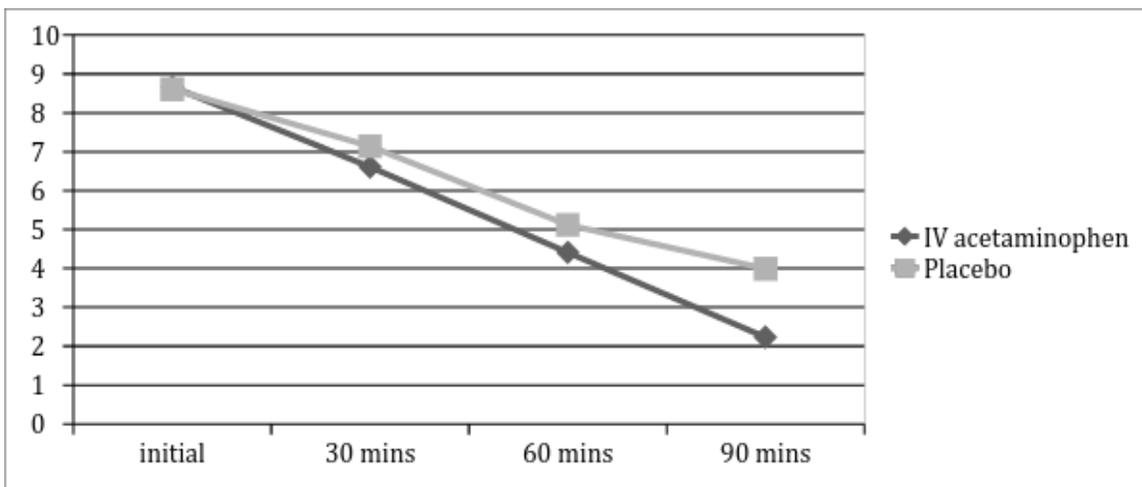


Figure 6. Mean reduction in pain at predefined intervals from time of patient arrival in IV acetaminophen and placebo arms.

Mean length of stay was approximately 186 minutes for the acetaminophen arm and 226 minutes for the placebo arm (Fig 6). Time to disposition and overall length of stay (LOS) were decreased in the Acetaminophen arm by a mean of 36.6 minutes when compared to placebo. Length of stay was extrapolated from the time to disposition entered in the electronic health record (EHR) and included (in both groups) additional rescue medications and additional reassessment times. The maximum LOS for either treatment arm was 361 minutes.

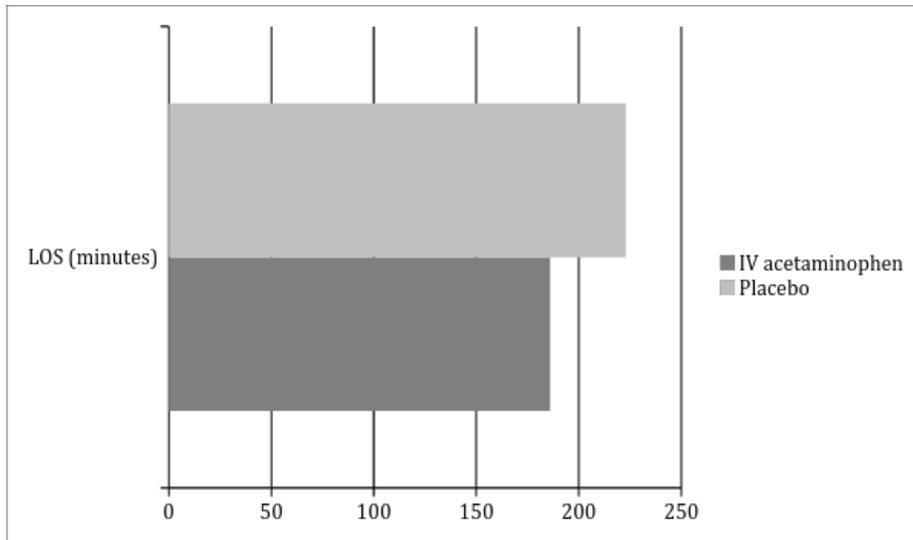


Figure 7. Mean total length of stay between IV acetaminophen and Placebo

Discussion

Treatment of headaches in the clinical setting is difficult and requires an evidence-based and often patient tailored approach, as there is a paucity of published data suggesting optimal migraine therapy²⁹. The American Headache society recommendations have endorsed certain medications as effective for various headache presentations including triptans, ergotamine derivatives, NSAIDs, opioids, and combination medications^{12,32}. As of late, there has been a significant driving force in the medical community to reduce the application of opiates in settings where multi-modal therapies may be used in its place^{3,11}. Narcotics used routinely in headache presentations are not widely considered standard monotherapy, as they can contribute to rebound effects, increased reliance and addiction^{12,29}. Colman et al discovered a significantly increased likelihood of patient return to the emergency department within seven days ($p=0.011$) with first-line narcotic treatment of headache³⁵. Several adverse effects are associated with opioid monotherapy to include allergic reactions, sedation, confusion or altered mental status, respiratory depression, hypotension, urinary retention, constipation, nausea and vomiting³. The limitations of narcotic medications include prolonged recovery times, increased length of hospital stay, and higher incurred costs to the institution when applied to postoperative pain management strategies. Using multi-modal therapy with additional agents helps to reduce the narcotic burden and thus this type of approach is likely to be beneficial to both physicians and patients' alike^{11,16}

Literature in current state is significant for several papers addressing the issue of multi-modal analgesia gaining recognition as an effective post-operative regimen for surgical patients. Clinical strategies utilizing parenteral acetaminophen as an adjunct have become increasingly popular as there are notable narcotic sparing effects demonstrated in surgical and anesthesia literature^{3-5,7-8,15-17,19,22-23} with minimal side effects and a low risk/benefit ratio⁴. Intravenous acetaminophen has a diverse and broad compatibility with other agents making it a successful adjunct to other agents, additional NSAIDs, and opiates¹⁵. It also synergistically has been shown to increase analgesic affect in multimodal analgesia^{15,18}.

Minimal literature is present regarding the narcotic sparing effects of parenteral acetaminophen outside of peri-operative settings⁷. To our knowledge, only one study exists in the emergency medicine literature investigating the use of parenteral acetaminophen. Bektas et al³² compared 1000mg IV paracetamol to morphine (0.1mg/kg) and placebo for the treatment of

renal colic in the emergency department. Mean pain reduction and rescue analgesia was similar to morphine, with a noted interesting trend in superiority in early pain assessment at fifteen minutes.

A recently published American headache society evidence assessment of migraine pharmacotherapies cited Level A evidence by Lipton et al demonstrating the efficacy of 1000mg of oral acetaminophen vs. placebo in treatment of acute migraine with regards to pain relief, functional disability, phonophobia, and photophobia²⁸, though the study population was limited to those with minimal nausea and need for bed rest. This is a select population of patients that are perhaps less likely to present to the emergency department for treatment, though the documented efficacy of acetaminophen is quite profound. A pharmaceutical sponsored study of OFIRMEV® (acetaminophen 1000mg/100ml cadence pharmaceuticals) demonstrated peak plasma and CSF concentrations were higher than oral acetaminophen ($P < 0.0001$) and rectal acetaminophen ($P < 0.0001$)^{13,14}. Additionally it does not undergo first pass metabolism in the liver thus reducing exposure of the liver to acetaminophen by half¹³ which may reduce the potential for hepatic injury^{13,20,22}. Additionally, the use of IV acetaminophen as primary therapy for headaches would decrease the pitfalls of using primary NSAIDs such as ketorolac or ibuprofen, in cases such as possible headache associated with intracranial hemorrhage where there is a platelet aggregation inhibition³⁴, potentially worsening clinical outcomes. Single doses of OFIRMEV® up to 3000 mg and repeated doses of 1000 mg every 6 hours for 48 hours have not been shown to cause a significant effect on platelet aggregation nor have any immediate or delayed effects on small vessels¹³.

Reviewing data findings, various pain scores were obtained in 30 minute intervals, of which, only the first 3 pain scores (after the initial assessment) for a total of 90 minutes post-medication administration were considered. Pain scores were reported on a 1-10 scale given the integration with the EHR and assistance with data collection and ease of nursing documented pain assessments essential to the study. We assessed for a 2 point decrease in Visual Analog System pain score as this is a commonly used measure in hospital settings for nursing and clinician pain score reporting³⁶.

Of the 90 patients sampled in the study, 46 reported their race as Black or African American, 43 as White, Hispanic or Caucasian, 1 as American Indian or Alaskan Native, with no Asian or Pacific Islander participants in the study. Religion and creed were not assessed. We can draw no statistically significant conclusions from this data other than a representation of our local population. The mean age of participants was 31 in males and 38 in females. This is consistent with reported headache sufferer demographics according to the American Headache Society.^{10,12,32} A significantly higher portion of women (70) when compared to men (20) were noted as participants in the study. This demographic trend is consistent with data published by the Agency for Healthcare Research and Quality who state women typically outnumber men 3:1 in terms of presenting to EDs seeking treatment for acute headaches.¹⁰

The definition of rescue medications administered in this study included narcotics, additional NSAIDs, orphenadrine, ergotamines, triptans or additional anti-emetics. Length of stay was extrapolated from the time to disposition entered electronically per the EHR and included in both groups additional rescue medications and additional reassessment times. Notably, it is unclear if participants treated with IV acetaminophen truly had a decreased length of stay secondary to the administration of the drug, or if this was an effect observed due to decreased utilization of rescue medications thus decreased time required in the emergency department. The maximum LOS for either treatment arm was 361 minutes in which the particular patient required significantly longer assessment due to refractory presentation. When compared to the additional subjects this was an outlier and did not greatly alter the data significance.

During enrollment, several physicians cited concern with excluding analgesic medications such as ketorolac from initial treatment. Several studies have demonstrated the superiority of combination metoclopramide plus diphenhydramine over NSAIDs^{26,30}. Regarding the efficacy of dopamine antagonist therapies for treatment of cephalgia, studies suggest a superiority of prochlorperazine to metoclopramide^{24,25,37} though Friedman et al³⁷ did not achieve statistical significance between treatment arms as opposed to prior studies. Diphenhydramine was administered to all patients due to the significantly reduced akathistic response with prophylactic administration.³¹ We believed the initial treatment regimen would be a reasonable and efficacious baseline regimen despite patients randomized to the placebo group not being given an NSAID medication upon initiation of treatment.

Some limitations were identified during trial completion. Our intention was to enroll a consecutive series of eligible patients, but this relied on both patient and physician participation and consent to trial participation, which were both factors not within controlled limits of the study. Based on the projected sample size to achieve appropriate power, a sample size of (n=100) was deemed optimal, due to exclusion criteria and other factors as noted before, a sample size of (n=90) was ultimately available for analysis. While the ultimate study population was smaller than initially intended, we observed a greater outcome effect than anticipated such that statistical significance was still achieved. Individual emergency medicine providers were encouraged to enroll all eligible patients according to the study protocol, however data displayed non-consecutive enrollment. We speculate this may be due to some provider reluctance to participate in the study or patient refusal preventing consecutive series enrollment. The degree of subject refusal was not recorded during the enrollment period for further reflection. At time of patient enrollment, treatment was initiated in both arms with initial administration of prochlorperazine and diphenhydramine within several minutes. In either arm, the 'study drug' required the blinded product to be sent from pharmacy to the Emergency Department, resulting in subsequent administration to the initial medications as noted above. The level of significance of this on study outcomes is difficult to determine, since as noted in the placebo group the time to significant pain score decrease was slower than the acetaminophen group, and pain score decrease more profound in the acetaminophen group, although both arms had delayed 'study drug' administration by up to 15 minutes post initial medications. To maximize our sample size and decrease exclusion burden, we did not target a specific subset of headache populations.

It would be beneficial to delineate in a larger trial if the observed benefit of IV acetaminophen is specific to certain headache conditions. Going forward, it would be worthwhile to study a head to head comparison of IV acetaminophen alone with a standard NSAID or opiate therapy to ascertain if similar efficacy exists in treatment of cephalgia as it was reported in treatment of renal colic by Bektas et al³³. Results may further support evidence suggesting avoidance of opiates in treatment of headache presentations is wise. It is also worthwhile to note that a cost analysis was not performed in this trial, which is important as OFIRMEV® as currently available in clinical practice does carry moderate increase in patient cost compared to therapies which have been traditionally utilized.

Based on results of this trial, Intravenous acetaminophen when used as an adjunct with prochlorperazine and diphenhydramine to treat acute headache presentations in the Emergency Department setting resulted in increased pain reduction, decreased length of stay, and less rescue medications including narcotics utilized when compared to prochlorperazine and diphenhydramine alone.

Acknowledgements

Grant funding provided by Michigan State University College of Osteopathic Medicine Statewide Campus System
Financial & Equipment Support provided by Lakeland Health.

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