

ASSESSMENT OF THE ANALGESIC EFFICACY OF INTRAVENOUS IBUPROFEN IN BILIARY COLIC

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ABSTRACT

Background: It is estimated over 20 million people aged 20-74 have gallbladder disease, with biliary colic being a common and painful symptom in these patients. Likely due to the relatively recent approval of intravenous ibuprofen use for fever and pain in adults, no assessment of its analgesic efficacy for biliary colic currently exists in the literature. In this double-blind, randomized, controlled trial we aim to assess the analgesic efficacy of intravenous (IV) ibuprofen given in the emergency department (ED) for the treatment of biliary colic.

Methods: Analgesic efficacy was evaluated using a visual analog scale (VAS) to assess for a decrease in pain scores. A VAS score decrease of 33% in relation to the VAS taken at the time of therapy drug administration was considered a minimum clinically important difference (MCID) in patient-perceived pain. A VAS was administered in triage upon enrollment, at the time of therapy administration, at 15-minute intervals during the first hour post-administration, and 30-minute intervals in the second hour. As the standard of care for suspected biliary colic at the study institution is administration of a one-time dose of IV morphine, patients were not denied initial morphine analgesia and were permitted to receive "rescue" morphine analgesia at any point during their ED course.

Results: A total of 22 patients completed the study. 9 were randomized to the IV ibuprofen arm, 9 to placebo, and 4 were excluded for a diagnosis other than biliary colic. Mean VAS values at time 0 to time 120 decreased from 5.78 to 2.31 in the ibuprofen group, and from 5.89 to 2.67 in the control group. There was no statistically significant difference in treatment status of ibuprofen vs. placebo (p-value (p.) 0.93), though there was a significant decrease in the measured VAS scores over time (0 minutes to 120 minutes, p.0.031) in both ibuprofen and placebo groups. A statistically significant and clinically important decrease in average VAS scores were seen in both placebo and ibuprofen groups (55% and 60%, respectively). There was no difference in time needed to achieve a clinically significant reduction in pain between groups.

Conclusion: The sample size of this study may be inadequate to fully assess the analgesic efficacy of IV ibuprofen for biliary colic. In the analysis group (n=18) no significant difference in treatment status of ibuprofen vs. placebo was seen, however there was a statistically and

clinically significant decrease in pain in both groups. Two potential confounding factors may have affected the trial's results: administration of standard-of-care IV morphine following initial triage assessment, and the inherent episodic and self-limited nature of biliary colic.

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I. INTRODUCTION & SIGNIFICANCE

Background:

Biliary colic

It is estimated that over 20 million people aged 20-74 have gallbladder disease (cholelithiasis or cholecystectomy) in the United States.¹ Biliary colic (BC) is a common symptom of gallstone disease, and is thought to originate from an outflow tract obstruction, resulting in visceral and somatic pain due to muscular spasm of the gallbladder wall.² Constant and severe pain is often experienced in the right upper quadrant or epigastric regions of the abdomen and may last for 2-3+ hours. In several studies BC has been shown to develop in approximately 25-30% of cholelithiasis patients over a 10-year period.³ Often presenting to the ED, patients with BC frequently require rapid administration of analgesics.

Treatment options include non-steroidal anti-inflammatory drugs (NSAIDs) or opioids, with NSAIDs having several potential advantages over the latter. Opioids carry the potential for abuse, produce respiratory depression, sedation, and can interfere with hepatobiliary scintigraphy (HIDA).⁴ Consequently non-opioids and NSAIDs have been extensively studied in the treatment of biliary colic, with a number of analgesics proving effective in treating moderate to severe pain.⁴⁻⁵ This study will continue the trend of assessing the analgesic effectiveness of NSAIDs by examining intravenous ibuprofen use for biliary colic in the ED.

Intravenous ibuprofen

In 2009, the US FDA approved intravenous ibuprofen (Caldolor®) for the management of mild to moderate pain, moderate to severe pain as an adjunct to opioid analgesics, and treatment of fever in adults.⁶ Intravenous ibuprofen is only the second approved intravenous NSAID available in the US, the other being ketorolac. As with other NSAIDs, ibuprofen's analgesic, anti-inflammatory, and antipyretic activity is thought to be achieved through direct binding and inhibition of cyclo-oxygenase (COX) enzymes.⁷ Additionally, ibuprofen is a racemic mixture, with the S-enantiomer being responsible for clinical activity.⁶ The R-enantiomer is thought to be a circulating reservoir for drug level maintenance, as it is proposed to be pharmacologically inactive and slowly and incompletely interconverts to the S-isomer.

Several randomized, double-blind, placebo-controlled, multicenter trials have assessed the efficacy of 400 and 800 mg doses of intravenous ibuprofen for its approved uses. In Southworth et al. and Kroll et al., adult elective abdominal or orthopaedic surgery patients and elective abdominal hysterectomy patients, respectively, were given 800 mg doses of intravenous ibuprofen postoperatively every 6 hours. Results demonstrated statistically significant analgesic and morphine-sparing effects.⁸⁻⁹ In a third study assessing pain with movement following orthopaedic surgery, a significant reduction in pain was noted following a 30 minute infusion of an 800 mg dose pre-operatively, and similar subsequent doses every 6 hours postoperatively.¹⁰ Additionally, three similarly designed studies have also shown intravenous ibuprofen to resolve fever to a significantly greater extent than placebo.¹¹⁻¹³

Intravenous ibuprofen represents an exciting and largely unexplored tool in pain management; its analgesic effectiveness in acute or postoperative settings is currently being investigated in a number of ongoing clinical trials. As a newly available intravenous NSAID, its application in biliary colic has likewise been unexplored. Compared to orally administered ibuprofen, the expected increase in maximum plasma concentrations (C_{max}) as well as faster time to reach these concentrations (t_{max}), the elimination of variability in efficacy due to variable absorption of oral ibuprofen by the gastrointestinal tract, and the potentially more reliable time of onset of analgesia, have all been noted as potential benefits of intravenous ibuprofen over the oral form.⁷ This is especially applicable to biliary colic patients presenting in the ED, where the reliability and speed of intravenous NSAID analgesia can present an alternative to oral or opioid alternatives.

Rationale & Goal:

Likely due to the relatively recent approval of intravenous ibuprofen use for fever and pain in adults, no assessment of its analgesic efficacy for biliary colic currently exists in the literature. Utilizing the VAS for pain, this study will address this lack of evidence and identify intravenous ibuprofen's value as a novel analgesic in the treatment of biliary colic. Though NSAID's have been extensively studied in the management of this phenomenon, this study aims

to help optimize pain treatment of biliary colic patients in the ED, and pave the way for future treatment comparison studies.

Hypothesis:

We hypothesize that intravenous ibuprofen will provide a clinically significant drop in self-reported patient pain levels as measured by VAS.

II. MATERIALS & METHODS

Study Design and Duration:

This is a double-blind prospective trial of intravenous ibuprofen for treatment of pain in adults presenting to the ED with biliary colic. Intravenous ibuprofen therapy will be compared to a saline-only control group. Subjects will complete a self-assessment of pain using a provided VAS on enrollment, every 15 minutes in the first hour following study therapy administration, and every 30 minutes in the second hour. On the condition that the patient has not left the ED following two hours, a VAS will be taken every hour until discharge or transfer.

Study Population:

Adults aged 18-55 presenting to the Maricopa Integrated Health System (MIHS) ED with right upper quadrant and epigastric abdominal pain suggestive of biliary colic will be asked to participate in this study. Enrolled patients included in the study analysis group will have radiographic evidence or history of gallstones, with patients diagnosed with other conditions being excluded.

Enrollment Criteria:

Patients were subjected to inclusion and exclusion criteria prior to enrollment in the trial (Table 1).

Study Procedures:

Upon patient presentation with signs and symptoms of biliary colic, a MIHS ED nurse will triage with an initial VAS. For initial temporary pain relief preceding study enrollment, 4 mg of morphine will be administered. Following obtaining consent to enroll in the study, a second VAS will be taken while the MIHS ED pharmacy randomizes study therapy - immediately preceding drug administration (time zero). Patients will be randomized to a placebo group or an ibuprofen intravenous 800 mg group. The intravenous ibuprofen will be mixed with 250 cc of normal saline, with an additional 250 cc saline added to the placebo group as well. Both groups will be infused over five minutes, and VAS scores will be taken post therapy administration every 15

minutes in the first hour, and every 30 minutes in the second hour (Figure 1). On the condition that the patient has not left the ED following two hours, a VAS will be taken every hour until discharge or transfer. Patients may receive rescue doses of morphine at the discretion of the treating provider. Patients will not be followed after discharge or transfer. Additionally, the safety of a five-minute infusion of intravenous ibuprofen will be assessed through any adverse drug events (ADEs) being noted simultaneously with every VAS administration. ADE symptoms monitored will include nausea, vomiting, skin rash, headache, dizziness, hemorrhage, and hypotension. Vital signs (temperature, heart rate, respirations, and blood pressure) will also be assessed at the time of every VAS administration

Result Interpretation and Statistical Analysis:

Analgesic efficacy was assessed through the use of VAS scores. A VAS score decrease of 33% in relation to the VAS taken at the time of therapy drug administration (time zero) was considered a clinically important difference, or “minimum clinical important difference” (MCID) in patient-perceived pain.¹⁴

In addition to compiling summary statistics, two-way Analysis of Variance with post hoc two-tailed, independent-samples *t*-tests and pairwise *t*-tests (with Bonferroni correction) were used to examine the effect of intravenous ibuprofen on patients’ self-reported pain scores. The between-subjects factor is considered to be Group (control vs. treatment), and the within-subjects factor to be Time (measured at four 15-minute intervals during the first interval and two half-hour intervals during the second hour). A total sample size of 36 (18 in each group) was determined to provide 80% power to detect a change of at least 33% in average pain scores at a given time point between the groups ($d = 0.96$) and between any two time points within each group ($dz = 0.70$). These estimates assume an alpha level of 0.05.¹⁵

TABLE 1. Enrollment criteria.

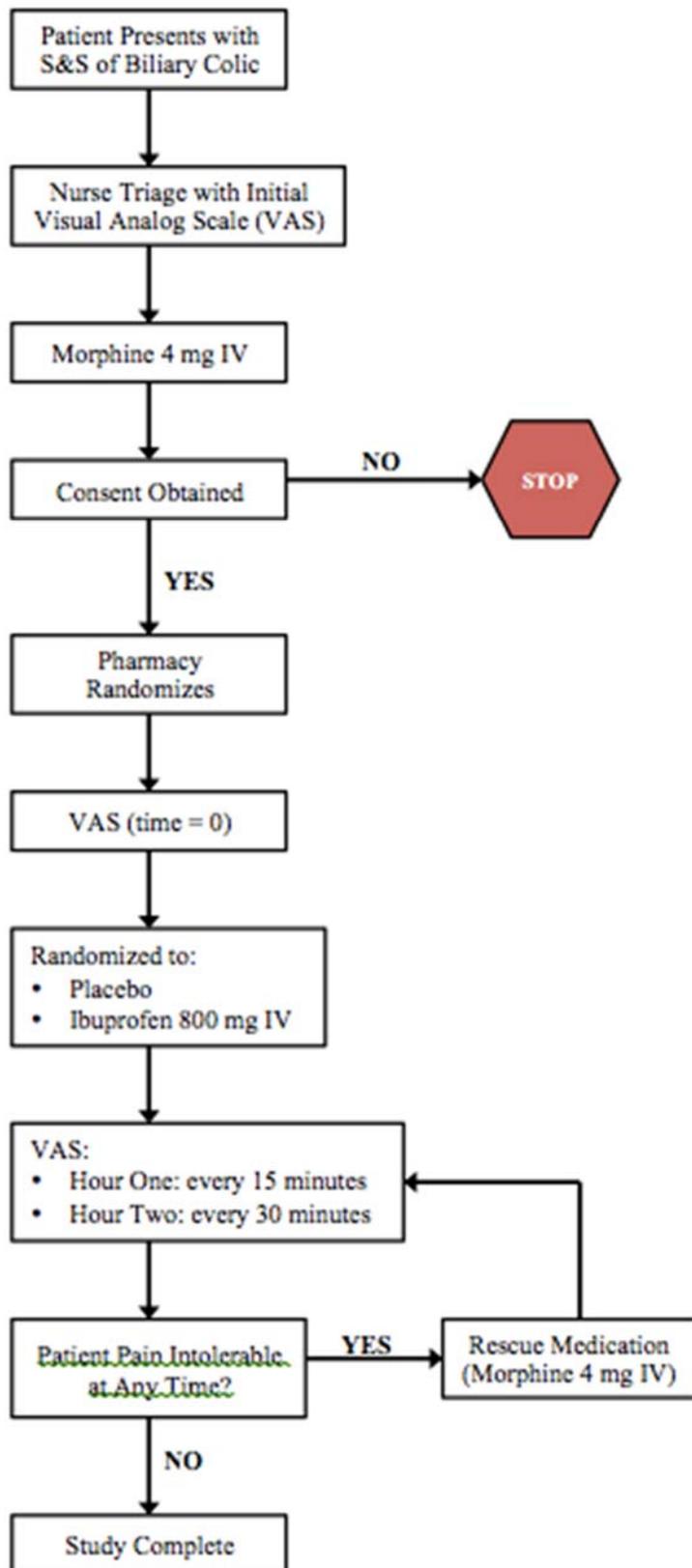
Inclusion Criteria

1. Patient age 18-55
 2. Present to ED with right upper quadrant (RUQ) abdominal pain
 3. Suspected diagnosis of biliary colic
 4. Negative pregnancy test for women of childbearing potential (complete POC testing form)
 5. No history of cholecystectomy
-

Exclusion Criteria

1. Patient age < 18 or > 55
 2. Incarcerated
 3. Hemodynamic instability
 4. Inability to reliably self-report or communicate pain intensity and pain relief
 5. Taking warfarin
 6. Cannot consent or are not competent to consent
 7. Hepatic, renal, cardiac failure
 8. NSAID or morphine allergy
 9. History of congenital bleeding diathesis or platelet dysfunction
 10. Peptic ulcer disease
 11. Are otherwise unsuitable for the study in the opinion of the investigator/sub-investigators
-

FIGURE 1. Study protocol summary.



III. RESULTS

A total of 22 of the 36 intended patients completed the study. 9 were randomized to the IV ibuprofen arm, 9 to placebo, and 4 were excluded for an imaging diagnosis other than biliary colic.

Mean VAS values at 0 and 120 minutes were 5.78 and 2.31 for the ibuprofen group and 5.89 and 2.67 for the control group. The MCID threshold, defined by a 33% decrease in initial VAS score, was correspondingly 3.85 and 3.92, respectfully (Table 3).

Two-way analysis of variance (ANOVA) demonstrated no statistically significant difference in treatment status of ibuprofen vs. placebo (p.0.93), though there was a significant decrease of VAS score from time point 0 to 120 (p.0.031) in both ibuprofen and placebo groups (Table 2). No association was found between time and treatment with regards to VAS score (p.0.97).

On average the treatment group was found to have a non-significant VAS score of 0.45 units lower than placebo (p.0.75), however a significant decrease of -3.2 VAS units from time point 0 to 120 minutes was seen in both placebo and ibuprofen arms (p.0.026, Table 4). A statistically significant and clinically important decrease (>33%) in mean VAS scores was seen in both placebo and ibuprofen groups (55% and 60%, respectively. Figure 3).

Additionally there was no difference in time necessary to achieve a MCID between both groups; a 33% reduction in VAS scores was met at 45-60 minutes in both arms (Figure 2).

Mean differences in VAS scores between ibuprofen and placebo groups at time point 0 and 120 minutes were assessed via linear regression (Table 5). At 120 minutes patients in the ibuprofen arm had a non-significant mean VAS score -0.18 units lower than placebo (p.0.89), versus -0.51 at time 0 (p.0.75).

TABLE 2. *Two-Way ANOVA*

Variables	P-Value¹
Treatment Status	0.93
Time	0.031
Treatment * Time Interaction	0.90

¹*P-values calculated using Two-way ANOVA.*

TABLE 3. Mean VAS values

<i>Time</i>	<i>Mean VAS score</i>
<i>Ibuprofen</i>	
0 minutes	5.78
MCID threshold ¹	3.85
120 minutes	2.31
<i>Control</i>	
0 minutes	5.89
MCID threshold	3.92
120 minutes	2.67

¹Minimum clinical difference (MCID) threshold defined by 33% decrease in initial t=0 VAS score

TABLE 4. Generalized Estimating Equation

Variables	Coefficient (95% CI)	P-Value ¹
Treatment		
Placebo	REF	0.75
Ibuprofen	-0.45 (-3.1, 2.4)	
Time		
0 min	REF	0.026
120 min	-3.2 (-6.0, -0.41)	
Treatment * Time Interaction	-0.052 (-4.1, 3.9)	0.97

¹P-Value calculated using the Generalizing Estimating Equation adjusting for age and gender.

TABLE 5. *Assessing the Mean Difference in VAS Scores between Ibuprofen and placebo via Linear Regression*

Variable	Time=0 Coefficient (95% CI)	P-Value¹	Time=120 Coefficient (95% CI)	P-Value²
Treatment				
Placebo	Ref	0.75	Ref	0.89
Ibuprofen	-0.51 (-3.9, 2.9)		-0.18 (-2.9, 2.6)	

¹P-Values calculated using Linear Regression at Time=0 adjusting for age and gender.

²P-Values calculated using Linear Regression at Time=120 min adjusting for age, gender and baseline VAS Scores.

FIGURE 2. Change in mean VAS scores over time for ibuprofen and control groups

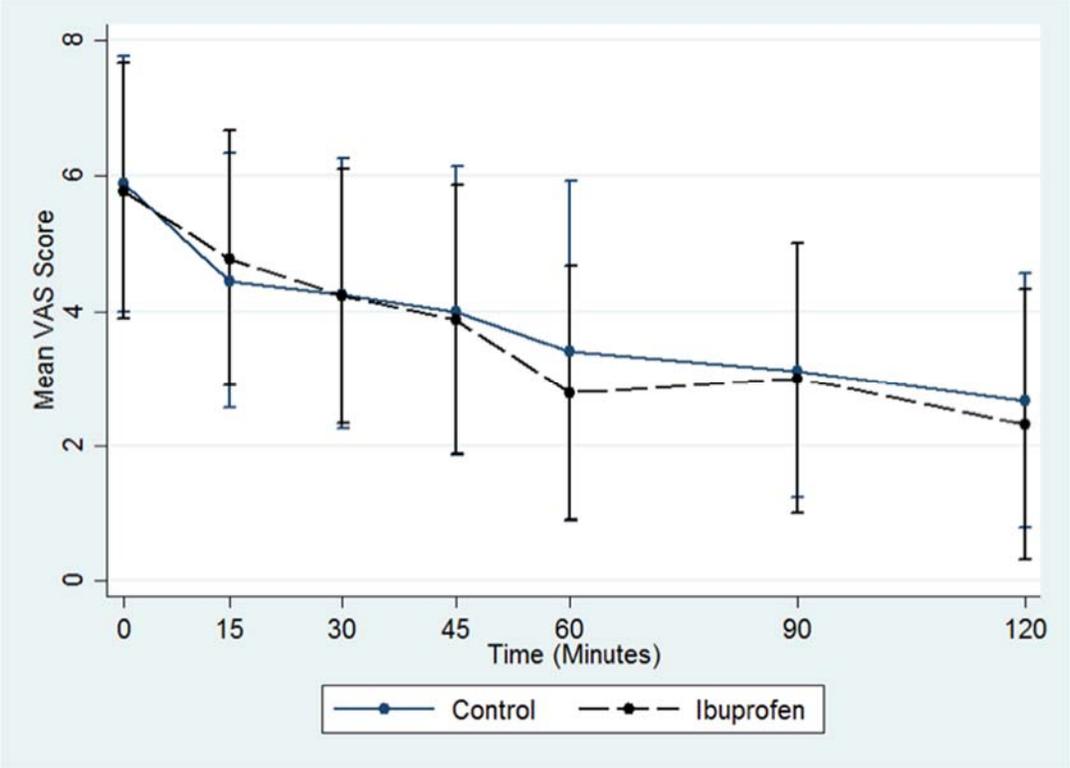
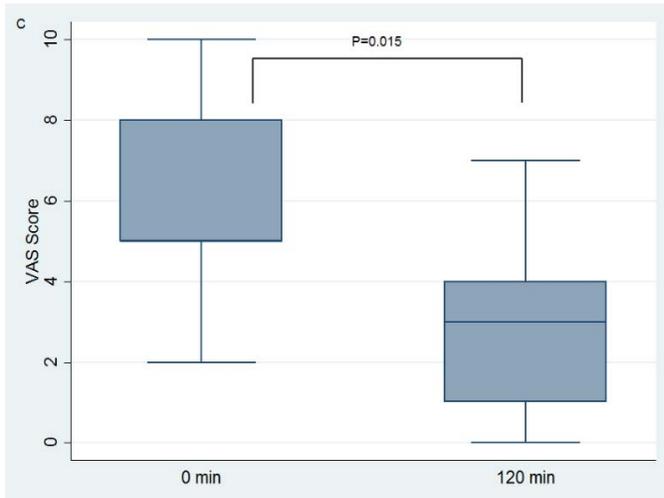
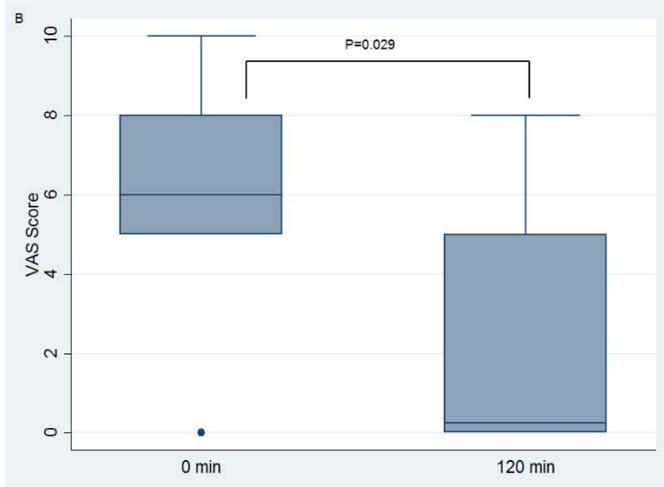
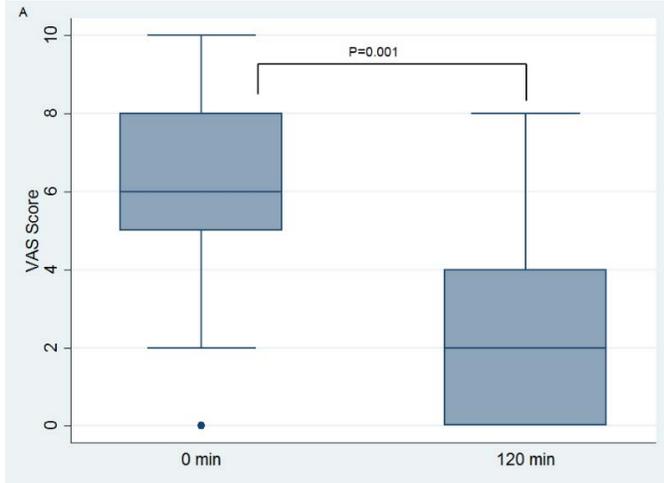


FIGURE 3. Change in VAS Score between Time=0 and 120 minutes Post-Treatment Administration in the A) Overall, B) Treatment Group, and C) Placebo Group



IV. DISCUSSION

The aim of this trial was to assess the analgesic efficacy of IV ibuprofen administered in the ED for the treatment of biliary colic. Currently no assessment of IV ibuprofen's utilization in this manner exists in the literature, with opioids and IV ketorolac being the standard of care in many hospital settings. Although we set out to optimize pain treatment of biliary colic by potentially identifying an alternative analgesic, our sample size was inadequate to fully assess the efficacy of IV ibuprofen. No significant difference in treatment status of ibuprofen vs. placebo was seen in our analysis group (n=18), however there was a statistically and clinically significant decrease in pain in both groups, defined as a decrease in mean VAS score of greater than 33%.

The chief limitation of the study is our inadequate sample size – 22 of 36 goal patients were enrolled – however two potential confounding factors may have additionally affected our results. A one-time dose of IV morphine was administered to patients following initial triage assessment – both as standard of care at the study institution and for ethical purposes. IV morphine sulfate is estimated to have a half-life of 1-5-4.5 hours and an analgesic duration of up to 7 hours¹⁶; given this duration, we cannot rule out that the statistically significant decrease in both ibuprofen and placebo VAS scores was due to initial morphine administration. Secondly, the decrease in pain observed across both groups may be related to the inherent episodic and self-limited nature of biliary colic. Given a patient's time course of symptom onset to presentation, followed by ED evaluation and enrollment, it is possible that an episode of biliary colic could resolve during the multiple hour hospital course regardless of treatment or placebo status. Ultimately, given the combination of a statistically significant decrease in pain in both groups, with no difference found in treatment status, an external confounding factor decreasing pain in both groups cannot be ruled out.

VI. CONCLUSION

The sample size of this trial may be inadequate to fully assess the analgesic efficacy of IV ibuprofen for biliary colic. In the analysis group no significant difference in treatment status of ibuprofen vs. placebo was seen, however there was a statistically and clinically significant decrease in pain in both groups. Two potential confounding factors may have affected the trial's results: administration of standard-of-care IV morphine following initial triage assessment, and the inherent episodic and self-limited nature of biliary colic. Further studies are indicated to better elucidate the role of IV ibuprofen in the treatment of biliary colic in the ED.

VII. REFERENCES

1. Everhart JE, Khare M, Hill M, Maurer KR. Prevalence and ethnic differences in gallbladder disease in the United States. *Gastroenterology* 1999; 117:632
2. Newman DH, Wolfson AB. *Analgesia for the biliary colic patient*. Emergency Sedation and Pain Management. Cambridge University Press; 2008. Pp. 131-4
3. Colli A, Conte D, Valle SD, Sciola V, Fraquelli M. Meta-analysis: nonsteroidal anti-inflammatory drugs in biliary colic. *Aliment Pharmacol Ther*. 2012 Jun;35(12):1370-8
4. Olsen JC, McGrath NA, Schwarz DG, Cutcliffe BJ, Stern JL. A double-blind randomized clinical trial evaluating the analgesic efficacy of ketorolac versus butorphanol for patients with suspected biliary colic in the emergency department. *Acad Emerg Med* 2008;15(8):718e22.
5. Henderson SO, Swadron S, Newton E. Comparison of intravenous ketorolac and meperidine in the treatment of biliary colic. *J Emerg Med* 2002;23(3):237e41.
6. Caldolor (ibuprofen) injection, for intravenous use: US prescribing information. Nashville (TN): Cumberland Pharmaceuticals Inc., 2009
7. Smith HS, Voss B. Pharmacokinetics of intravenous ibuprofen: implications of time of infusion in the treatment of pain and fever. *Drugs* 2012; 72 (3): 327-37
8. Southworth S, Peters J, Rock A, et al. A multicenter, randomized, double-blind, placebo-controlled trial of intravenous ibuprofen 400 and 800 mg every 6 hours in the management of postoperative pain. *Clin Ther* 2009 Sep; 31 (9): 1922-35
9. Kroll PB, Meadows L, Rock A, et al. A multicenter, randomized, double-blind, placebo-controlled trial of intravenous ibuprofen (i.v.-ibuprofen) in the management of postoperative pain following abdominal hysterectomy. *Pain Pract* 2011 Jan-Feb; 11 (1): 23-32
10. Singla N, Rock A, Pavliv L. A multi-center, randomized, double-blind placebo-controlled trial of intravenous ibuprofen (IV-ibuprofen) for treatment of pain in postoperative orthopedic adult patients. *Pain Med* 2010 Aug; 11 (8): 1284-93
11. Morris PE, Promes JT, Guntupalli KK, et al. A multicenter, randomized, double-blind, parallel, placebocontrolled trial to evaluate the efficacy, safety, and pharmacokinetics of intravenous ibuprofen for the treatment of fever in critically ill and non-critically ill adults. *Crit Care* 2010; 14 (3): R125

12. Krudsood S, Tangpukdee N, Wilairatana P, et al. Intravenous ibuprofen (IV-ibuprofen) controls fever effectively in adults with acute uncomplicated Plasmodium falciparum malaria but prolongs parasitemia. *Am J Trop Med Hyg* 2010 Jul; 83 (1): 51-5
13. Promes JT, Safcsak K, Pavliv L, et al. A prospective, multicenter, randomized, double-blind trial of IV ibuprofen for treatment of fever and pain in burn patients. *J Burn Care Res* 2011 Jan-Feb; 32 (1): 79-90
14. Jensen MP, Chen C, Brugger AM. Interpretation of visual analog scale ratings and change scores: a reanalysis of two clinical trials of postoperative pain. *J Pain*. 2003 Sep; 4 (7): 407-14
15. Erdfelder E, Faul F, Buchner A. GPOWER: a general power analysis program. *Behavior Research Methods, Instruments, and Computers* 1996; 28, 1-11
16. AHFS drug information 2006. McEvoy GK, ed. Morphine sulfate. Bethesda, MD: American Society of Health-System Pharmacists; 2006;2117-24