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PROJECT TITLE:

Assessment of the analgesic efficacy of intravenous ibuprofen in biliary colic

PRINCIPAL INVESTIGATOR:

Dan Quan, DO

Email: dquan@email.arizona.edu

Phone: (602) 344 5058

Fax: (602) 344 1208

MEDICAL STUDENT:

Kenneth Zurcher, UA College of Medicine-Phoenix, Class of 2017

Email: Zurcher@email.arizona.edu

Phone: (650)703-6561

PROJECT PERFORMANCE SITE:

Maricopa Integrated Health System (MIHS) Emergency Department

Address: 2601 E. Roosevelt St. Floor 1. Phoenix, AZ, 85008.

Table of Contents

1. ABSTRACT	3
2. RESEARCH QUESTION	3
3. INTRODUCTION AND RATIONALE	3
4. METHODOLOGY	5
4.1 <i>OBJECTIVE</i>	5
4.2 <i>STUDY DESIGN AND DURATION</i>	5
4.3 <i>STUDY POPULATION</i>	5
4.4 <i>ENROLLMENT CRITERIA</i>	5
4.5 <i>STUDY PROCEDURES</i>	6
4.6 <i>RESULT INTERPRETATION AND STATISTICAL ANALYSIS</i>	6
4.7 <i>POTENTIAL COMPLICATIONS AND ETHICAL CONSIDERATIONS</i>	7
5. OBJECTIVE / DISCUSSION	7
6. RESOURCES	7
7. DISCONTINUATION / WITHDAWAL CRITERIA	8
8. ADVERSE EVENTS	8
9. BUDGET / SPONSORS	8
10. CASE REPORT FORMS	8
11. REFERENCES	9

1. ABSTRACT

The aim of this study is to assess the analgesic efficacy of intravenous ibuprofen given in the emergency department (ED) for the treatment of biliary colic. 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.

Utilizing a visual analog scale (VAS) for patient self-assessment of pain, this study will address this lack of evidence and identify intravenous ibuprofen's value as a novel analgesic in administration, at 15-minute intervals during the first hour post-administration, and 30-minute intervals in the second hour. Though NSAID's have been extensively studied in the management of this phenomenon, this study aims to help optimize pain treatment of patients presenting to the ED with biliary colic, and potentially pave the way for future analgesic treatment comparison studies.

2. RESEARCH QUESTION

The aim of this study is to assess the analgesic efficacy of intravenous ibuprofen given in the ED for the treatment of biliary colic. We hypothesize that intravenous ibuprofen will provide a clinically significant drop in self-reported patient pain levels as measured by VAS.

3. INTRODUCTION AND RATIONALE

Biliary colic

It is estimated that over 20 million people aged 20-74 have gallbladder disease (gallstones or cholecystectomy) in the United States.¹ Biliary colic (BC) is a common symptom of gallstone disease, and it 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 800mg 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

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.

4. METHODOLOGY

4.1 Objective

The aim of this study is to assess the analgesic efficacy of intravenous ibuprofen given in the ED for biliary colic.

4.2 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 at predetermined intervals for a minimum of two hours. A VAS will be taken 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.

4.3 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.

4.4 Enrollment Criteria

Inclusion Criteria:

- Patient age 18-55
- Present to ED with right upper quadrant (RUQ) abdominal pain
- Suspected diagnosis of biliary colic
- Negative pregnancy test for women of child-bearing potential (complete POC testing form)
- No history of cholecystectomy

Exclusion Criteria:

- Patient age <18 or >55
- Incarcerated
- Hemodynamic instability
- Inability to reliably self-report or communicate pain intensity and pain relief
- Taking warfarin
- Cannot consent or are not competent to consent
- Hepatic, renal, cardiac failure
- NSAID or morphine allergy
- History of congenital bleeding diathesis or platelet dysfunction

- Peptic ulcer disease
- Are otherwise unsuitable for the study in the opinion of the investigator/sub-investigators

4.5 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, 4mg 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). Patient will be randomized to a placebo group or an ibuprofen intravenous 800mg group. The intravenous ibuprofen will be mixed with 250cc or 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. On the condition that the patient has not left the ED following 2 hours, a VAS will be taken every hour until discharge or transfer. Patient 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.

4.6 Result Interpretation and Statistical Analysis

Analgesic efficacy will be 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) will be considered a clinically important difference in patient-perceived pain.¹⁴

In addition to compiling summary statistics, we will use a two-way Analysis of Variance with post hoc two-tailed, independent-samples *t*-tests and pairwise *t*-tests (with Bonferroni correction) to examine the effect of intravenous ibuprofen on patients' self-reported pain scores. The between-subjects factor will be Group (control vs. treatment), and the within-subjects factor will be Time (measured at four 15 minute intervals during the first interval and two half-hour intervals during the second hour). We will need a total sample size of 36 (18 in each group) to provide the 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 ($d_z=0.70$). These estimates assume an alpha level of 0.05.¹⁵ All results, from both descriptive and inferential analysis, will be presented in table and/or graphical format.

4.7 Potential Complications and Ethical Considerations

Potential complications include an inability to enroll enough patients to satisfy power calculations and achieve statistical significance. As this is a therapy drug vs. placebo study and biliary colic is a common presentation in the MIHS ED, we do not foresee this as being a significant complication.

All NSAIDs carry a similar side effect profile, including nausea, vomiting, skin rash, headache, dizziness, hemorrhage, and hypotension. Pain control and potential adverse drug effects will be monitored through the use of the VAS and pain assessment forms, respectively. Vital signs, including temperature, heart rate, respirations, and blood pressure will also be taken at every VAS administration. An ethical issue taken into considerations is the pain potentially experienced by patients randomized to placebo. As mentioned previously rescue opioids may be administered at the discretion of the treating physician if a patient's pain is not well controlled.

5. OBJECTIVE / DISCUSSION

The aim of this study is to assess the analgesic efficacy of intravenous ibuprofen given in the ED for the treatment of biliary colic. Currently no assessment of intravenous ibuprofen's analgesic efficacy in patients with biliary colic exists in the literature, likely due to its recent approval for use in fever and pain in adults. This study will address this lack of evidence and identify intravenous ibuprofen's value as a novel analgesic in the treatment of biliary colic. Prior to intravenous ibuprofen, the only other approved intravenous NSAID available in the United States has been intravenous ketorolac. As such, intravenous ketorolac has been a staple of biliary colic treatment. This study aims to help optimized pain treatment of biliary colic patients in the ED by potentially providing an alternative analgesic. If intravenous ibuprofen is indeed shown to be effective this study seeks to pave the way for future treatment comparison studies. Additionally, intravenous analgesia provides an added benefit in patients who present with nausea and vomiting where oral medications may otherwise prove ineffective.

6. RESOURCES

All work for this study will be conducted at the Maricopa Integrated Health System (MIHS) ED under the guidance of Dr. Dan Quan. The Maricopa Medical Center (MMC) is located in Maricopa County, Arizona, and features advanced medical services including adult emergency care. The MMC houses a level I Trauma Center and Emergency Center, with approximately 50,000 patients receiving urgent and emergency care each year. The MIHS ED is actively involved in research as has compensated research staff and assistants available to enroll patients approximately 20 hours daily. The presence of ED triage nurses will allow for efficient screening and enrollment of potential study participants. Additionally we will have access to an MIHS biostatistician—Andr  Valdez, PhD., who will be performing statistical analyses for the study.

7. DISCONTINUATION / WITHDRAWAL CRITERIA

The principal investigator or treating physician may withdraw a subject from the study at any time they feel it is in the subject's best interest, or for any other reason. All subjects may voluntarily withdraw their participation in the study at any time without any change in further treatment.

8. ADVERSE EVENTS

All NSAIDs—including IV ibuprofen—carry a similar side effect profile, including nausea, vomiting, skin rash, headache, dizziness, hemorrhage, and hypotension. Pain control and potential adverse drug effects will be monitored through the use of the VAS and pain assessment forms, respectively. Vital signs, including temperature, heart rate, respirations, and blood pressure will also be taken at every VAS administration. Every patient will receive at least one dose of morphine, and further morphine may be administered at the discretion of the treating physician if a patient's pain is not well controlled.

8.1 Serious Adverse Event Reporting

All serious adverse events will be reported to the IRB within 24 hours after the investigator or study personnel are made aware of the serious adverse event in accordance with the IRB adverse event reporting guidelines.

All adverse events and serious adverse events will be followed until resolution or until the principal investigator deems the event to be chronic or the subject to be stable. Adverse event and serious adverse event follow-up may be done by phone, unless physical follow-up is deemed necessary by the principal investigator.

9. BUDGET / SPONSORS

Study drug (IV ibuprofen) will be provided by Cumberland Pharmaceuticals.

10. CASE REPORT FORMS

A case report form will be completed for each subject that has signed and informed consent form and participated in the study. The form will include pain assessments, ADE's, vital signs, as well as diagnosis and exclusion information.

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- INCLUSION CRITERIA**
- Patient age 18-55
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- EXCLUSION CRITERIA**
- Patient age < 18 or > 55
 - Incarcerated
 - Hemodynamic instability
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