DELRAY Medical Center

STUDY PROTOCOL TITLE: Assessing the Efficacy of IV ibuprofen for Treatment of Pain in Orthopedic Trauma Patients.

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BACKGROUND AND SIGNIFICANCE

Critically ill patients may experience pain related to their underlying illness, trauma, disease processes, surgery or other non-surgical interventions (Tietze, 2012). The primary goal of analgesia is optimizing patient comfort in conjunction with balancing the negative physiologic responses to pain including hypermetabolism, increased oxygen consumption, hypercoagulability, and alterations in immune function (Tietze, 2012). Acute pain is defined as a, "complex, unpleasant experience with emotional and cognitive, as well as sensory, features that occur in response to tissue trauma" (American Pain Society, 2012, p. 10).

Uncontrolled or poorly managed pain leads to serious medical complications; impairs recovery from injury or procedures; negatively impacts quality of life; progresses to chronic pain, and increases morbidity, mortality and length of ICU or hospital stay (Malchow & Black, 2008). A number of studies indicate a high incidence of untreated pain in ICU settings (Malchow & Black, 2008). Payen et al. (2007) demonstrated in a recent study that 90% of ICU patients were treated with opioids; whereas, only 42% were assessed for pain. In addition, procedural analgesics and nonopioid adjuncts were only used approximately one third of the time. The reluctance to offer pain medication within the acute care setting is understandable and multifactorial.

Evaluation and treatment of pain in trauma patients is complicated by the patient's pathologic condition, the effects of medications, and the diverse interventions used in patient care (Freire, Afessa, Cawley, Phelps, & Bridges, 2002). Several authors suggest trauma complications such as hypovolemia, coagulopathies, and head and spinal cord injuries actually hinder administration of adequate pain control for fear that analgesics will cause further adverse physiological events in these patients (Lovrincevic, Kotob, & Santarosa, 2005; Chanques et al., 2006) Trauma exerts pervasive effects on a multitude of body systems, specifically making this population more susceptible to the side effects of analgesics or sedative drugs (Chanques et al., 2006). Health care providers are; therefore, more cautious and limited in their choice of opioid medications.

Acute pain is more difficult to manage and control if permitted to become severe; making prompt, preemptive, and adequate treatment imperative (APS, 2012). Acute pain is most often nociceptive responding to non-opioids and opioids. Pharmacological management

is the cornerstone of acute pain management with opioids being the most commonly prescribed class of medications and the mainstay of management in the acute care setting. Opioid analgesics exert their effects by binding to receptors in the central and peripheral nervous system and the gastrointestinal tract. The use of opioids; however, is often limited due to related adverse side effects including sedation, respiratory depression, nausea and vomiting, constipation, hallucinations, confusion, sedation, and allergic reactions (Bookstaver, 2010). Their use has also been linked to compromised function of the immune system.

Opioids are useful in mitigating the sensation of pain but provide no benefits to the underlying disease process (Sinatra & Jahr, 2011). Adjunctive agents for pain including non-steroidal anti-inflammatory agents (NSAIDS) may be used in combination with opioids to mitigate the side effects of both agents by reducing the total dose required. The APS (2012) advocates the use of multimodal analgesia including non steroidal anti-inflammatory agents (NSAIDS) for optimal pain control in the treatment of acute traumatic pain. The rationale behind multimodal therapy is to capitalize on the synergistic action between pharmacological agents and different techniques.

The potential side effects of opioids especially in the trauma population combined with recommendations for a synergistic approach to pain management suggests medications such as IV i~~I~~buprofen may be beneficial in treating pain in trauma patients. Additionally, intravenous (IV) medications are preferred in critically ill patients because gastrointestinal (GI)dysfunction can lead to unpredictable absorption of medications given orally (Tietze, 2012). Multi-modal therapy can help avoid common complications of opioid-centered analgesia including physical dependence, addiction, and respiratory depression (Malchow & Black, 2008).

IV ibuprofen was approved for use in the United States in June of 2009 and it is indicated for management of mild to moderate pain, management of moderate to severe pain as an adjunct to opioid analgesics, and reduction of fever (Sinatra & Jahr, 2011). Similar to oral ibuprofen, the IV formulation can inhibit both COX-1 and COX-2. IV ibuprofen has more 'balanced' affinity for the COX isoenzymes. In key clinical trials, bleeding gastric and renal events were similar to placebo. This has significant implications for the clinical use of IV i~~I~~buprofen. IV Caldolor is also available on the formulary of Delray Medical Center and has been available since late 2009.

The efficacy and safety ~~of IV~~of IV ibuprofen related to pain management has mainly been studied with post-operative orthopedic patients. Southworth, Peters, Rock and Pavliv (2009) conducted a multi-center, randomized, double-blind placebo-controlled dose-ranging study to assess the effects of IV ibuprofen ~~vs~~ versus placebo in 406 patients undergoing orthopedic or abdominal surgery. IV ibuprofen at a dose of 800mg was associated with reduced morphine use during the first 24 hours (p=0.030) and significant reductions in pain at rest and with movement. Another study done by Kroll, Meadows, Rock, and Pavliv (2011) was a multi-center, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of IV ibuprofen at the initiation of wound closure. IV i~~I~~buprofen was continued for 8 doses and then as needed every 6

hours for up to 5 days following surgery. IV ibuprofen was associated with a reduction in morphine requirements over the first 24 hours and resulted in a significant reduction in pain at rest and with movement. As with the dose-ranging study there was no difference in treatment-emergent AE's, including nausea and flatulence, between the study groups. Singla, Rock and Pavliv (2010) conducted a multi-center, randomized, double-blind placebo-controlled trial of IV ~~I~~ibuprofen for treatment of pain in post-operative orthopedic adult patients. Pre and post operative administration of IV ibuprofen significantly reduced both pain and morphine use in orthopedic surgery patients in this study.

Multiple studies done with orthopedic patients have demonstrated the efficacy of using IV ibuprofen for treatment of acute pain leading to significant reductions in pain and decreased use of narcotics. Additionally, Orlando Regional Medical Center a Level I trauma center conducted a retrospective study of IV ibuprofen and traumatic rib fracture. The study demonstrated that early IV ibuprofen therapy with traumatic rib fractures significantly decreases narcotic requirements and resulted in clinically significant decreases in hospital length of stay. The authors suggest IV ibuprofen should be given upon admission to augment pain control and recommend a prospective study.

STUDY OBJECTIVES:

1. To evaluate the effectiveness of around the clock (OTC) IV ibuprofen (8 doses) in decreasing pain in orthopedic trauma patients with fractures of the extremities, face, pelvis and/or ribs compared to patients not receiving the medication.
2. To evaluate the effectiveness of around the clock (OTC) IV ibuprofen (8 doses) in decreasing the use of opioid analgesics among orthopedic trauma patients with fractures of the extremities, face, pelvis, and/or ribs compared to ~~compared to~~ patients not receiving the medication.

SELECTION OF STUDY POPULATION:

The goal is to enroll approximately 67 patients in each group for a total of 134 patients. However, the study will be reevaluated after 3 months to determine if this number needs to be reconsidered.

Inclusion Criteria:

1. Trauma patient admitted to Trauma ICU or Trauma Step-Down Units.
2. Fracture of ribs, face, extremities and/or pelvis
3. Age between 18 and 75 years old
4. Adequate IV access
5. Able to self report and communicate pain severity

Exclusion Criteria:

1. History of allergy or hypersensitivity to any component of IV i~~I~~buprofen, aspirin (or aspirin related products) NSAIDs, or COX-2 inhibitors

2. Any intracranial or spinal cord trauma
3. History of clinically significant bleeding disorders including ITP, DIC or platelet dysfunction
4. Recent history of intracranial surgery or stroke (within past 30 days)
5. History of ulcers, gastritis or previous GI bleeding
6. Renal Impairment (Creatinine > 3.0 mg/dL)
7. Pregnant or breastfeeding
8. Otherwise unsuitable in the opinion of the treating physician at time of randomization.

Withdrawal of Subjects from the Study

A good faith effort will be made to ensure that all subjects complete the study through day five, consistent with the provisions of informed consent and good clinical judgment in respect to safety. The following are potential reasons to terminate the participation of the subject in the study:

- The subject's health would be jeopardized by continued participation.
- Withdrawal of consent: subject decides to stop participation in the study for any reason, or is unable to complete the study as described.

STUDY DESIGN

Patients who meet all the inclusion criteria and do not meet any exclusion criteria (see above) will be consented and randomized by the research team . team. All individuals who are part of the research team will work under the direct supervision of the PI, are responsible for completing NIH or other demonstration of completion of a course in Good Clinical Practice training in addition to Delray Medical Center's (DMC) specific research training including confidentiality and compliance requirements.

Once the patient has been identified as an eligible candidate for the study based on the inclusion/exclusion criteria the research team will confirm with the treating physician that there are no other factors preventing the patient from being enrolled in the study. The inclusion/exclusion (I/E) sheet is completed and initialed by the treating physician and by the member of the research team. The patient is then approached for informed consent. Once the patient has signed the informed consent, a copy is will be provided to the patient and , one is will be placed in the chart (per hospital protocol). The signed I/E sheet is placed in a designated IV iIbuprofen binder within each unit.

Once the patient has signed the informed consent and the I/E sheet has been completed, the research team member will place the order set (already created and made available to the research team) in the computer under Dr. Weisz (PI) as protocol orders. The orders will include a pharmacy consult and will , bbe flagged as a study protocol. Study ProtocolT and the research team member will also be responsible for notifying pharmacy that there is a newly consented research patient. The pharmacy has a pre-generated numbers list used to randomize patients. The numbers are listed on the spreadsheet in

athe random order and patients are assigned a number as they are enrolled in the study. Everyone besides theWith the exception of the research staff including pharmacy, the PI, study coordinator, trauma nurses and the nurse researcher working with patients, all others will be blinded as to who receives IV Iibuprofen. The study can be unblinded at any time during the study in the event of patient complications or other extenuating circumstances. IV bags will be labeled as IV iIbuprofen when they are sent to the trauma units making the placebo and medication bags appear the same..

The Trauma Research Nursetrauma nurse(s) isswill be responsible for retrieving the collected information from the binder and keeping track of research patients and collectingstudy data through day five. The patient once enrolled in the study will have pain measured using either a Visual Analog Scale (VAS)/FACES or a Numerical Rating Scale (NRS). The FACES Sscale verbal assessment ranges from 0 (no hurtpain) to 10 (worste pain imaginablepossible pain) and the NRS ranges from 0 (nNo pain) to 10 (wWorst pPossible pPain). A baseline pain score will be obtained prior to administering either the placebo or the IV iIbuprofen. Additional pain medication will be provided as per Standardized IV iIbuprofen Order Set. The patient will then have pain assessed as per hospital specific protocol within the trauma units. Additionally pain should be assessed prior to and following administration of any pain medication. For the purposes of the study, pain assessments will be obtained for both groups from nurse charting at hHours 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, & 48 and then twice daily for a total of five days. A pain score may be obtained from the nursing documentation if it has been done within + or – two hours of the times stated above.

Sixty-seven patients will receive the placebo and 67 patients will receive the IV iIbuprofen based on a random numbering system per pharmacy. There is just one order set entered into the computer at this time; patients will receive the same prn pain medications and IV Pepcid dosage regardless of whether they are in the placebo or the IV iIbuprofen group. All patients will receive a total of 8 doses of the medication or the placebo (800mg IV iIbuprofen/placebo over 30 minutes) along with 20 mg IV/po Pepcid for 48 hours.

IV Ibuprofen Order Set

I. Around the Clock Medications

a. IV iIbuprofen 800mg IV Q6 hours (x 8 doses)
b. Pepcid 20mg po or IV BID

II. PRN Medications

Administration of pain medications are based on the patient's self assessment of pain using a Visual Analog Scale (VAS)/FACES (0-10) or Numerical Rating Scale (NRS) (0-10). Patient must be able to self report pain.

A. **Minimal Pain (Rated as a 1-2)**

- Tylenol 650mg po/pr prn Q4h

B. Minimal-Moderate Pain (3-4)

- Oxycodone 5mg 1 tab po ~~q 4~~Q4h

C. Moderate Pain (5-6)

- Oxycodone 10mg po ~~q~~4Q4h
- Morphine 1mg IV Q4h

D. Moderate-Severe Pain (7-8)

- Morphine Sulfate 2mg IV Q3h
- Dilaudid 1mg IV Q4h
- May give 1 tab of Oxycodone 5mg po Q4h for breakthrough pain

E. Severe Pain (9-10)

- Morphine Sulfate 4mg IV Q3
- Dilaudid 2mg IV Q3
- May give 1 tab of Oxycodone 5mg po Q4h for breakthrough pain

***IV Caldolor 400-800mg can be given every 6 hours prn for pain after the 48 hour time period at the discretion of the treating MD.**

The patient should not be given any pain medications if the patient is known to have an existing allergy to that medication.

Primary Endpoints

- Decrease in reported pain using the FACES or Numerical Rating Scale NRS) during the initial 48 hour time period
- Decrease in the use of opioid medications during the initial 48 hour period.

Secondary Endpoints

- Decrease in reported pain using the FACES or Numerical Rating Scale (NRS) over a five day time period
- Decrease in the use of opioid medications over a five day time period.
- Decrease in hospital and ICU length of stay
- Rate of treatment failure (defined as the requirement of additional pain medications within the 48 hour window).

Information that may be gathered about the patient include age, race, type of injuries, co-morbidities, medical history, self-reported pain levels, lab values, vital signs, type and amount of narcotic pain medications, length of hospital stay, patient outcomes, continued use of IV ibuprofen and other factors which in the opinion of the investigator may be significant to the study.

Charts will be flagged should a patient need to go to surgery or the operating room (OR); indicating the patient is on the IV i~~I~~buprofen Study. An attempt will be made to maintain

a standardized OR sedation medication regimen for these patients and to resume the standardized prn pain medication order set per protocol upon return to the trauma units.

The study drug IV ibuprofen has been approved by the FDA in the United States since June of 2009 and is indicated for management of mild to moderate pain, management of moderate to severe pain as an adjunct to opioid analgesics, and reduction of fever (Sinatra & Jahr, 2011). It has been used and approved for use in trauma and acute care patients and is on the formulary at our facility since late 2009. The administration of Pepcid to all trauma patients is a standard prophylaxis for prevention of GI complications given within our trauma unit.

The goal of this study is not to assess the pharmacokinetics of IV ibuprofen as a drug which has been determined by the FDA, but to determine its efficacy in managing pain in a particular subset of patients; i.e. that of trauma patients with fractures of the extremities, pelvis and/or ribs. The patients are assessed by the trauma surgeons during daily rounds and notified of the medications the patient is currently taking. Should there be any changes in lab values, patient status or condition the trauma surgeons will assess the patient as they would any other patient who had been given this medication for treatment of pain or medical condition and make appropriate clinical decisions. The trauma surgeons are made aware that the patient is in the study via rounds and through the computerized charting system.

To supplement safety for research patients, the PI and Research Coordinator will monitor daily vital signs, intake and output and lab work upon admission, Day 1, Day 2 and Day 5 with special attention paid to consistent elevated blood pressure, elevated creatinine clearance (>3,0 mg/dL), anemia (decreased Hgb, Hct, RBC), fluid retention, edema, increased bleeding times (PT, PTT & INR), significantly elevated liver enzymes (ALT, AST) and signs and symptoms of GI bleeding (abdominal pain or cramping, blood streaked stools, constipation, melena or coffee ground emesis). It should be noted that most adverse events associated with IV Ibuprofen are related to extended or long term use; whereas, this protocol involves only 8 doses of the medication. The information collected and monitored by the research team will include those tests done as standard of care procedures and not for the specific purposes of the research; therefore some results may not be obtained but data will be included if it is within + or – 3 days after completion of the study (Day 5) .

Unexpected Problems (~~AE's and SAE's)~~Adverse Events (AE's) or Serious Adverse Events (SAE's)

The risks associated with taking this medication are clearly outlined in the informed consent. Serious risks include cardiovascular thrombotic events; heart attacks; strokes and GI bleeding, ulceration or perforation of the stomach or intestines. Other common risks may include allergic reaction, edema; hypertension; exfoliative dermatitis, fluid retention, anemia, increased bleeding time, other GI side effects like nausea/vomiting, diarrhea or

abdominal pain; and elevated liver enzymes. All these symptoms have been identified by the FDA as risks.

Unexpected problems that are adverse events (AE's) or serious adverse events (SAE's) will be reported through 3 days post infusion (Days 1-5) and in accordance with hospital policy and WIRB reporting requirements for unanticipated or unexpected problems upon review by the Principal Investigator within 10 working days of the time the investigator becomes aware of them.

DATA STORAGE AND ANALYSIS:

Data will be entered into an Excel spreadsheet. Data will be kept confidential at all times. Safeguards to ensure confidentiality will include National Institutes of Health (NIH) or Collaborative Institutional Training Initiative (CITI) -Good Clinical Practice (GCP) training by study personnel, maintaining the data in a password protected site, and securing all hardware that would contain any files with PHI. All findings and reported data will be de-identified.

REGULATORY AND PROCEDUREAL REQUIREMENTS

Good Clinical Practice (GCP) is the international ethical and scientific quality standard for designing, conducting, recording and reporting studies that involve the participation of human subjects. This study will be conducted in compliance with GCP and the applicable national regulations so as to assure that the rights, safety, and well being of the participating study subjects are protected and consistent with the ethical principles that have their origin in the Declaration of Helsinki.

The Investigator (according to national provisions) is responsible for following the regional law where the study is to be conducted to obtain written approval for the clinical study protocol (including all substantial protocol amendments), the subjects informed consent (including written assent, when applicable), informed consent updates, subject recruitment procedures (e.g., advertisements) and any other information to be provided to subjects from an Institutional Ethics Committee (IEC)/Institutional Review Board (IRB) that complies with the local regulatory requirements.

Written approval of the study must be obtained from the IRB prior to the study being implemented. Copies of approval documentation will be maintained by both the Investigator and authorized representative in the designated study documentation files.

As patients in this study may not be able to provide informed consent at baseline due to clinical status, informed consent will be obtained following the regional law where the study is being conducted, under the guidance of the IRB while remaining fully compliant with International Conference on Harmonisation (ICH) guidelines.

The investigator is responsible for assuring the appropriate content of the informed consent form (ICF) and that informed consent is obtained from each subject in

accordance with the applicable local regulations and guidelines. The original ~~singed~~ signed informed consent is to be retained in the study documentation files. The subject's medical records should also document that the informed consent form was signed and dated and that the appropriate local legal requirements regarding informed consent were followed.

The Investigator or designated person(s) will give the subject information about the study in a form that the subject can read and understand. If the subject is unable to read, oral information on the study will need to be provided to the subject in the presence of a witness, if applicable, according to regional law. The subject will be informed that he/she ~~could~~ may withdraw ~~form~~ from the trial at any time, for any reason, without risk to their treatment plan or medical care.

RESULTS

Statistical analysis will be done primarily using IBM SPSS Statistical Software; occasionally other software may be used.

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