A DOUBLE-BLINDED RANDOMIZED TRIAL OF IV IBUPROFEN AND MORPHINE COMBINATION THERAPY IN PATIENTS PRESENTING TO THE EMERGENCY DEPARTMENT WITH RENAL COLIC

A Thesis submitted to the University of Arizona College of Medicine -- Phoenix
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Calliandra Hintzen
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Mentor: Dan Quan, DO

Background/Abstract:

Renal stones (or "calculi") are a relatively common condition, affecting up to 12 percent of people during their lifetime. Typical presentation of renal calculi is acute, intermittent flank pain, termed "renal colic", which may radiate to the groin. Pain may be accompanied by hematuria, nausea, or vomiting.[1] Acute renal colic is a common cause for presentation to the Emergency Department, accounting for an estimated 1 million emergency room visits annually in the United States.[2] The severe pain associated with renal calculi requires immediate analgesia, and effective analgesia is associated with improved functional capacity after drug administration.[3]

In this trial, we compare the efficacy of IV ketorolac vs. IV ibuprofen for pain control in patients with renal colic in a three-armed double-blind prospective trial. Patients were randomized to one of three treatment groups, receiving parenteral infusions of either IV ibuprofen + morphine, IV ketorolac + morphine, or morphine monotherapy. Outcome of drug administration was measured by patients' self-assessment of pain on a verbal scale at 15 mins, 30 mins, 60 min, and 120 min after drug administration. We hypothesized that IV ibuprofen would provide effective, non-opioid pain relief in the emergency setting and might have a lower incidence of adverse effects than ketorolac. Need for rescue analgesia (with 4 mg morphine) was observed as an indirect measure of analgesic efficacy.

A total of 11 patients completed the study. There was no significant difference in area under the curve of pain score in any of the three treatment arms ($p>0.4$). The ibuprofen group demonstrated consistent improvement in pain over the course of 120 min of study, with 100% of the patients in that arm demonstrating downtrending pain scores. Though the sample size was too small to identify a statistically significant difference in need for rescue medication, there was a trend toward increased opioid in the ibuprofen group, with 50% of those participants receiving rescue analgesia with morphine.

The sample size of this pilot study is inadequate to fully assess the analgesic efficacy of IV ibuprofen for renal colic. A trend toward improved pain control in the ibuprofen group was observed, with 100% of the patients in the ibuprofen arm reporting decreased pain after 120

minutes (as compared to 66% in the ketorolac arm and 75% in the placebo arm). Further study of efficacy and need for rescue analgesia is warranted.

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1.0 SIGNIFICANCE

The most commonly prescribed analgesic regimen in renal colic is morphine with intravenous (IV) ketorolac.[6] The paired parenteral administration of opioid analgesics with non-steroidal anti-inflammatory drugs (NSAIDs) offers the advantage of rapid analgesic effect while minimizing the necessary opioid dose in order to limit adverse drug effects. IV NSAIDs, including ibuprofen, have previously been shown to be opioid-sparing in acute pain patients and in the perioperative setting, thereby minimizing the incidence of hypotension, nausea, vomiting, and dizziness commonly experienced with opioid analgesic administration.[7]

The recent development of intravenous ibuprofen (Caldolor), and preliminary evidence suggesting a favorable side effect profile, warrants an examination of its efficacy and tolerability as compared to the current standard of care. The primary endpoint of our study will be determining the analgesic efficacy of an IV ibuprofen + morphine regimen as compared to IV ketorolac + morphine.

NSAIDs act through inhibition of cyclooxygenase enzymes, of which there are two subtypes, COX-1 and COX-2. COX-1 is renoprotective, gastroprotective, and involved in platelet activation. COX-2 is pro-inflammatory and the therapeutic benefit of NSAIDs is thought to be derived mainly from their inhibition of COX-2. Both ibuprofen and ketorolac are COX inhibitors, but ibuprofen is over 100 times more COX-2 selective than ketorolac, with a COX-2/COX-1 inhibition ratio of 0.4 versus 0.003, respectively.[8] It is has been suggested that greater COX-2 specificity is associated with lower risk of GI bleeding— a major adverse drug event common to all COX inhibitors.[9] Ibuprofen may therefore prove to have a lower incidence of bleeding events than ketorolac. However, recent studies of COX-2 specific inhibitors, drugs like celecoxib and rofecoxib, suggest a higher risk of cardiovascular adverse drug events (ADEs), like thrombosis and myocardial infarction, in COX-2 specific NSAIDs than in other NSAIDs.[8] Preliminary investigations of IV ibuprofen have shown a lower than expected incidence of ADEs in small sample groups, with no statistically significant increase in rates of GI bleeds, cardiovascular ADEs, renal toxicity, or thrombotic events in IV ibuprofen treatment groups as compared to placebo, but further investigation is required to establish differences in the side effect profile of

IV ibuprofen versus other NSAIDs.[9] Therefore, ADEs constituted a secondary endpoint of our study.

Singla et al. found that a pre-operative dose of IV ibuprofen reduced early post-operative pain scores (on a visual analog scale) by 13.9% with movement, and 15.8% at rest as compared to placebo, with no statistically significant difference in ADEs between treatment groups.[10] This preliminary evidence suggests that IV ibuprofen is safe to administer to individuals who may shortly need surgical intervention. As ketorolac carries a black-box warning against pre-operative administration, IV ibuprofen provides an appealing alternative for analgesia in patients presenting with acute renal colic, for whom treatment may in rare cases involve surgical measures.[11]

Both ketorolac and ibuprofen have been shown to be opioid-sparing, and recent literature found no therapeutic difference in analgesia achieved in patients with renal colic by ketorolac alone versus meperidine alone in either single-dose or titrated dosing regimens.[3, 12] This emerging evidence supports the use of NSAIDs alone or NSAIDs with opioid rescue analgesia for treatment of renal colic in the future. Should IV ibuprofen prove as effective as ketorolac, it would be an optimal candidate for monotherapy in the future, providing effective pain management without ADEs associated with opioid use. Our study aimed to determine the analgesic efficacy and safety of intravenous ibuprofen with morphine as compared to intravenous ketorolac with morphine and morphine alone in patients presenting to the emergency department with renal colic.

2.0 OBJECTIVES

To determine the analgesic efficacy and safety of intravenous ibuprofen with morphine as compared to intravenous ketorolac with morphine and morphine alone in patients presenting to the ED with renal colic.

2.1 Hypothesis: IV ibuprofen + morphine is as effective at controlling pain in patients with renal colic as the currently used analgesic regimen (IV ketorolac + morphine).

3.0 METHODS

This was a three-armed observer-blinded prospective trial of intravenous ibuprofen with morphine for treatment of pain in adults presenting to the Emergency Department with renal colic. The study therapy was compared to the standard of care and a morphine-only control group. This study was approved by the institutional review board at Maricopa Medical Center and the University of Arizona.

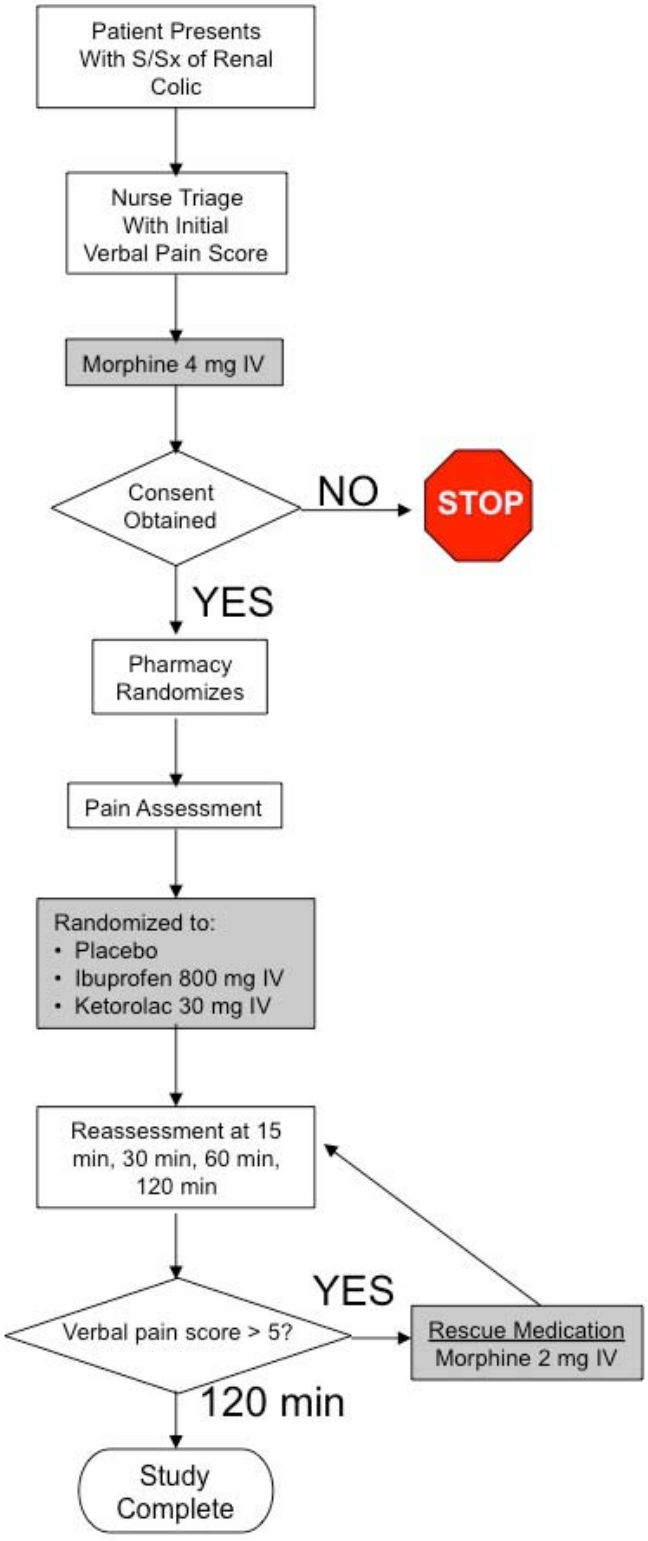
3.1 Study Design:

Patients who met eligibility criteria and did not meet exclusion criteria were randomized to one of three treatment arms: morphine monotherapy, ketorolac + morphine, or ibuprofen + morphine. Treatment assignment was blinded. All patients received 4 mg IV morphine, then study drug (ketorolac, ibuprofen, or placebo) was infused over five (5) minutes. All patients were informed of the triple-arm study design and had rescue analgesia with 4 mg IV morphine available.

Verbal pain score and vital signs were measured at the time of drug administration (t=0 min), then reassessed at 15 minutes, 30 minutes, 60 minutes, and 120 minutes following drug infusion. Patients were also asked about known side effects of analgesia at each pain assessment. Any symptoms identified that were new since initial presentation were noted as adverse drug events. Incidence of treatment failure, i.e. the need for rescue analgesia, was included as an additional measurement of efficacy.

TABLE 1
Inclusion Criteria
1. Age 18-55 years, presenting with renal colic 2. Signed informed consent
Exclusion Criteria
1. Age younger than 18 years or older than 55 years 2. Pregnancy 3. Hemodynamic instability 4. Inability to reliably self-report or communicate pain intensity and pain relief 5. Current therapy with warfarin, lithium, or combination of ACE-inhibitors and furosemide 6. Inability to consent 7. Known hepatic, renal, or cardiac failure 8. Known NSAID or opioid allergy 9. Therapy with an analgesic within 6 hours 10. History of congenital bleeding diathesis or platelet dysfunction 11. Unsuitability for the study in the opinion of the investigator

FIGURE 1: Study protocol.



3.2 Patient Population:

The trial was conducted in the emergency department at Maricopa Medical Center (Phoenix, AZ). Adults 18-55 presenting to the Emergency Department with acute flank pain and a suspected diagnosis of renal colic were enrolled in the study. Patients included in the study either had a history of documented kidney stones or radiographic evidence of a kidney stone or hydronephrosis. (Note: any subject patients that were ultimately diagnosed with another condition were removed from the analysis group.)

3.3 Analysis Methods:

Data from historical studies on IV ibuprofen were utilized for sample size calculations. A sample size of 6 patients per group provided 80% power to detect a 10% difference in area under the curve (AUC) of pain score with an alpha level of 0.05. Sample size estimates were done using NCSS/PASS software (NCSS, Kaysville, UT).

The AUC of pain scores from 0 to 120 minutes was determined for each treatment arm and compared using analysis of variance (ANOVA). The trapezoidal rule was used to calculate the AUC of each pain curve. Any missing pain measurements were estimated by linear interpolation from surrounding data points.

Frequency of rescue analgesia utilization in each group was to be compared using a chi-square test, but actual sample sizes proved too small for such analysis.

4.0 RESULTS

16 patients in total were enrolled. Five (5) patients voluntarily discontinued participation or were ultimately excluded from the study because they were not diagnosed with renal calculi. A total of 11 patients completed the study. Patients were randomized to treatment groups for a total of 4 participants in the placebo (morphine monotherapy) group, 3 in the ketorolac + morphine group, and 4 in the ibuprofen + morphine group.

ANOVA demonstrated no significant difference in AUC of pain assessed in any of the three treatment arms ($p>0.4$, $F=0.95$). Further analysis with 2-way ANOVA demonstrated no significant interaction between time after drug administration, drug administered, and pain scores (p.0.7, $F=0.33$; $p>0.3$, $F=1.13$).

The ibuprofen group demonstrated consistent improvement in pain score over the course of 120 min of study, with 100% of the patients in that arm demonstrating downtrending pain scores. ANOVA detected no significant difference between treatment groups in pain scores at 120 minutes (as a percentage of initial pain) ($p>0.7$, $F=0.35$).

Though the sample size was too small to identify a statistically significant difference in need for rescue medication, there was a trend toward increased opioid use in the ibuprofen group, with 50% of those participants receiving rescue analgesia with morphine. One adverse drug event was reported and was characterized by nausea in a single patient in the placebo arm.

FIGURE 2: Verbal pain score over time as a percentage of baseline pain score.

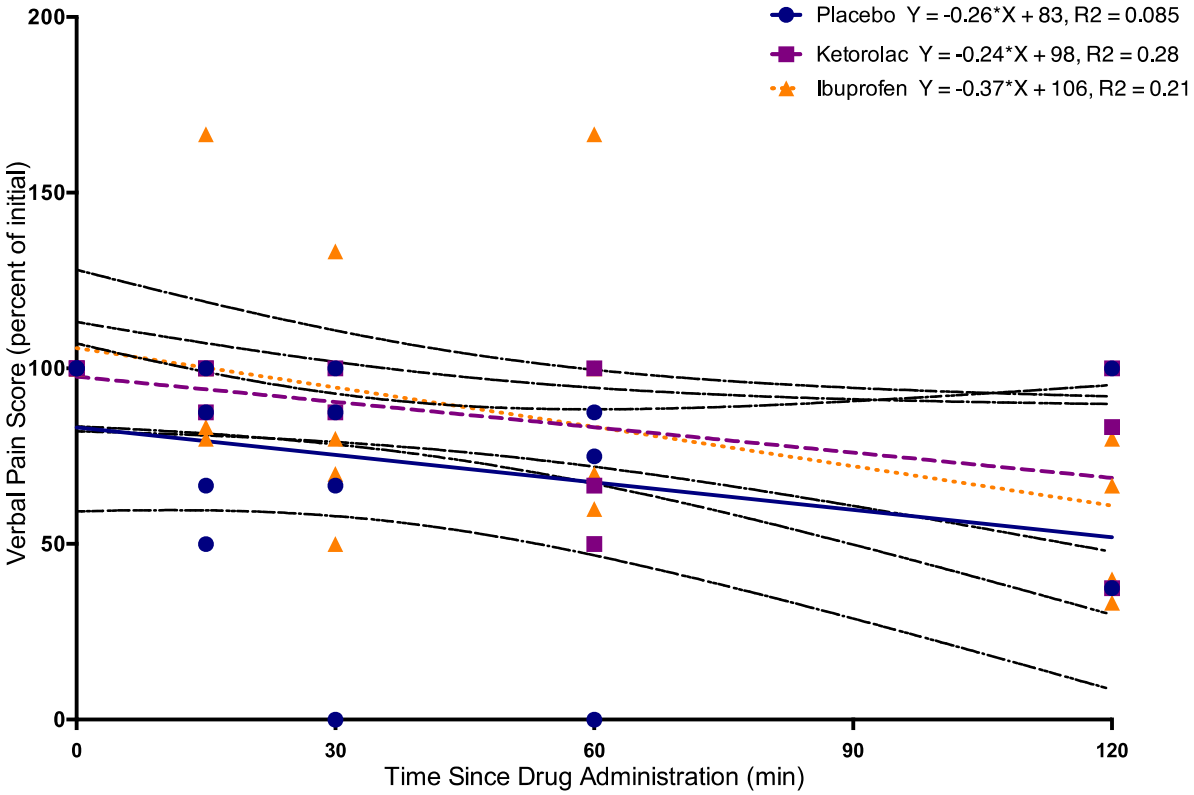
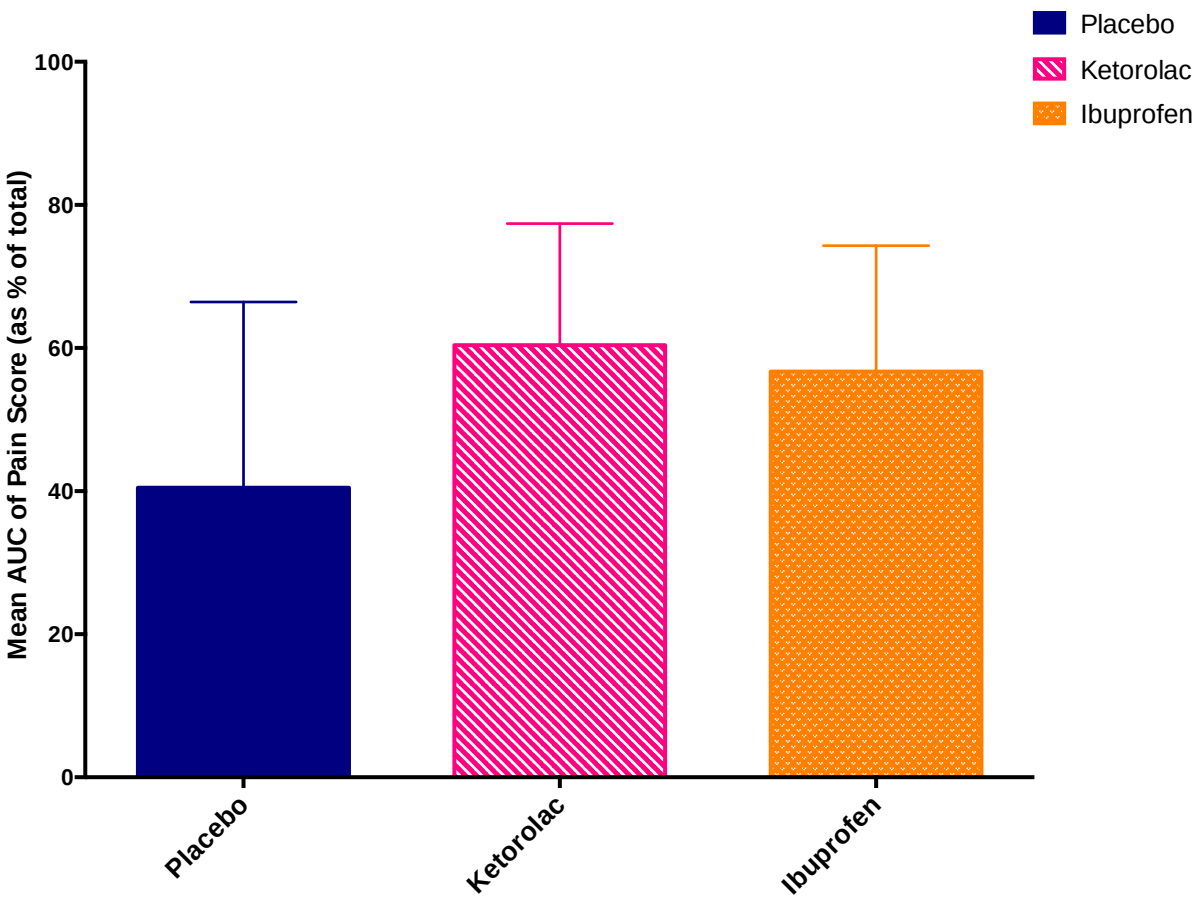


FIGURE 3: Mean area under curve of pain score in each treatment group.



5.0 DISCUSSION

Previous randomized controlled trials have demonstrated the opioid-sparing effect of IV NSAIDs for analgesia in renal colic.[6] The sample size of this pilot study is inadequate to fully assess the analgesic efficacy of IV ibuprofen for renal colic. All treatment groups demonstrated improvement in median pain scores (corrected for pain at presentation) over the 120 minute observation period. A statistically insignificant trend toward improved pain control in the ibuprofen group was observed, with 100% of the patients in the ibuprofen arm reporting improved pain from baseline at the termination of the study (as compared to 66% in the ketorolac arm and 75% in the placebo arm).

There was no detectable difference in analgesic efficacy between treatment groups, and 2-way ANOVA demonstrated no relationship between treatment group, time after drug administration, and pain score. As some degree of interaction between drug administration and pain would be expected, it is likely that these results represent type II error arising from inadequate sample size rather than true equivalency between the medication regimens.

The ibuprofen group demonstrated an increased need for rescue analgesia, with 50% (n=2) of the participants in the ibuprofen group utilizing rescue morphine, versus 0% in the other treatment groups. Possible explanations for this phenomenon include delayed onset of action versus ketorolac, less analgesic efficacy as compared to ketorolac, or a type I error.

The chief limitation of this study is that inadequate sample size renders it underpowered to draw significant conclusion about the comparative efficacy of the treatments studied.

Given prior success with NSAIDs in the treatment of renal colic, further study to definitively demonstrate the efficacy of IV ibuprofen for this indication is warranted. This study did not seek to demonstrate the overall safety of IV ibuprofen, which has been FDA approved and previously shown to be safe for perioperative analgesia.[10]

6.0 CONCLUSION

IV ibuprofen may be an effective analgesic in renal colic. This three-arm randomized control trial was inadequately powered to determine if a combination IV ibuprofen + morphine therapy was comparable to the current standard (ketorolac + morphine) or to morphine alone. Patients in all three treatment arms exhibited improvement in median pain scores (corrected for pain at presentation) over the 120 minute observation period. Patients who received ibuprofen demonstrated a consistent decrease in pain score over time, but also requested rescue analgesia more often than patients receiving ketorolac + morphine or morphine monotherapy. These preliminary findings and historical success with combination IV NSAID + opioid therapy indicate that IV ibuprofen has potential as an analgesic for renal colic. Further study is indicated to elucidate what role this novel drug will play in the treatment of renal colic and whether or not it represents an improvement over the current standard of care.

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