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E. Nominated By: Jim Stevermer
F. Institutional Affiliation of Nominator: University of Missouri
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H. Identified Through: Evidence Updates
I. PURLs Editor Reviewing Nominated Potential PURL: Corey Lyon
J. Nomination Decision Date: 2/15/2017
K. Potential PURL Review Form (PPRF) Type: RCT
L. Assigned Potential PURL Reviewer: Corey Lyon
M. Reviewer Affiliation: University of Colorado
A. Abstract: STUDY OBJECTIVE:
Nonsteroidal anti-inflammatory drugs are used extensively for the management of acute and chronic pain, with ketorolac tromethamine being one of the most frequently used parenteral analgesics in the emergency department (ED). The drugs may commonly be used at doses above their analgesic ceiling, offering no incremental analgesic advantage while potentially adding risk of harm. We evaluate the analgesic efficacy of 3 doses of intravenous ketorolac in ED patients with acute pain.

METHODS:
We conducted a randomized, double-blind trial to assess the analgesic efficacy of 3 doses of intravenous ketorolac (10, 15, and 30 mg) in patients aged 18 to 65 years and presenting to the ED with moderate to severe acute pain, defined by a numeric rating scale score greater than or equal to 5. We excluded patients with peptic ulcer disease, gastrointestinal hemorrhage, renal or hepatic insufficiency, allergies to nonsteroidal anti-inflammatory drugs, pregnancy or breastfeeding, systolic blood pressure less than 90 or greater than 180 mm Hg, and pulse rate less than 50 or greater than 150 beats/min. Primary outcome was pain reduction at 30 minutes. We recorded pain scores at baseline and up to 120 minutes. Intravenous morphine 0.1 mg/kg was administered as a rescue analgesic if subjects still desired additional pain medication at 30 minutes after the study drug was administered. Data analyses included mixed-model regression and ANOVA.

RESULTS:
We enrolled 240 subjects (80 in each dose group). At 30 minutes, substantial pain reduction was demonstrated without any differences between the groups (95% confidence intervals 4.5 to

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5.7 for the 10-mg group, 4.5 to 5.6 for the 15-mg group, and 4.2 to 5.4 for the 30-mg group). The mean numeric rating scale pain scores at baseline were 7.7, 7.5, and 7.8 and improved to 5.1, 5.0, and 4.8, respectively, at 30 minutes. Rates of rescue analgesia were similar, and there were no serious adverse events. Secondary outcomes showed similar rates of adverse effects per group, of which the most common were dizziness, nausea, and headache. 

CONCLUSION:
Ketorolac has similar analgesic efficacy at intravenous doses of 10, 15, and 30 mg, showing that intravenous ketorolac administered at the analgesic ceiling dose (10 mg) provided effective pain relief to ED patients with moderate to severe pain without increased adverse effects.

B. Pending PURL Review Date: 1/11/2018

SECTION 2: Critical Appraisal of Validity
[to be completed by the Potential PURL Reviewer]

A. Number of patients starting each arm of the study?
240 subjects
- 80 in the ketorolac 10 mg
- 80 in the ketorolac 15 mg
- 80 in the ketorolac 30 mg

B. Main characteristics of study patients (inclusions, exclusions, demographics, settings, etc.)
Setting: Emergency Department of a 711 bed urban hospital with 120,000 annual ED visits

Study: randomized, double-blind;

Inclusion:
- 18-65 years of age
- ED visit for pain with score of ≥5
- Would be given ketorolac per usual care

Exclusion
- > age 65
- Pregnancy or breastfeeding
- Active PUD or Gl hemorrhage
- Renal or hepatic insufficiency
- NSAID allergy
- Unstable vitals (BPs, pulse)
- Any other pain meds on board

Demographics
- The groups were similar in terms of demographic characteristics and baseline vital signs
- Mean ages and sex were 41.5, 40.1, and 38.8 years and 39%, 32%, and 37% men, respectively.
- Baseline numeric rating scale pain scores were equivalently high in all 3 study groups

C. Intervention(s) being investigated?
IV push of ketorolac 10 mg

D. Comparison treatment(s), placebo, or nothing?
Ketorlac 15 mg or 30 mg

E. Length of follow-up? (Note specified end points, e.g., death, cure, etc.)
   - pain scores, vital signs, and adverse effects at baseline and 15, 30, 60, 90, and 120 minutes

F. What outcome measures are used? List all that assess effectiveness.
   - Primary outcome = reduction in numeric pain score 30 minutes after ketorolac administration
   - Secondary outcomes = rates and percentages of subjects experiencing adverse effects and requiring rescue analgesia

G. What is the effect of the intervention(s)? Include absolute risk, relative risk, NNT, CU, p-values, etc.
   - At 30 minutes postadministration, subjects randomized to receive 10 mg of intravenous ketorolac improved from a mean pain numeric rating scale score at baseline of 7.7 to a mean score of 5.2 (difference=2.5), the 15-mg group improved from 7.5 to 5.1 (difference=2.4), and the 30-mg group improved from 7.8 to 4.8 (difference=3.0).
   - Reductions in pain scores from baseline to 30 minutes were statistically significant for all subjects. However, there were no differences in pain score reduction from baseline to 30 minutes across the 3 dose groups.
   - No differences in the mean numeric rating scale pain scores themselves between dose groups at 30 minutes.
   - The 95% confidence intervals for the ketorolac groups were similar: 4.6 to 5.8 for the 10-mg group, 4.5 to 5.6 for the 15-mg group, and 4.2 to 5.4 for the 30-mg group.

H. What are the adverse effects of intervention compared with no intervention?
   - The most commonly reported adverse effects were dizziness, nausea, and headache, with no differences across the 3 doses.

I. The study addresses an appropriate and clearly focused question.
   (select one) Well covered
   Comments:

J. Random allocation to comparison groups:
   (select one) Well covered
   Comments:

K. Concealed allocation to comparison groups:
   (select one) Well covered
   Comments:

L. Subjects and investigators kept “blind” to comparison group allocation:
   (select one) Adequately addressed
   Comments: Pharmacist unblinded but patients and providers were.

M. Comparison groups are similar at the start of the trial:
   (select one) Well covered
   Comments:

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N. Were there any differences between the groups/arms of the study other than the intervention under investigation? If yes, please indicate whether the differences are a potential source of bias. (select one)  
Adequately addressed  
Comments: Some differences in terms of chief complaints (headache in 1, 3, 9, in the 10, 15, 30 mg groups respectively) and duration of pain. States that baseline demographics were “similar” but there are no statistical analyses.

O. Were all relevant outcomes measured in a standardized, valid, and reliable way? (select one)  
Well covered  
Comments: Pain scales

P. Are patient oriented outcomes included? If yes, what are they?  
Pain scales are considered patient oriented, albeit somewhat subjective. Looking for an improvement in pain from baseline to post-treatment is appropriate.

Q. What percent dropped out, and were lost to follow up? Could this bias the results? How?  
At the 30 minute time frame (primary endpoint), only 2 patients were lost to follow up (one in the 10 mg, one in the 30 mg). This should not contribute to significant bias.

R. Was there an intention-to-treat analysis? If not, could this bias the results? How?  
Yes.

S. If a multi-site study, are results comparable for all sites?  
Single site – limitation to the study.

T. Is the funding for the trial a potential source of bias? If yes, what measures were taken to ensure scientific integrity?  
This research was funded in part by an unrestricted grant from the New York State Department of Health Empire Clinical Research Investigator Program and by the Maimonides Research and Development Foundation.  
Authors had no conflict of interest.  
Those that secured the grant were blinded and not involved in study medication preparation.

U. To which patients might the finding apply? Include patients in the study and other patients to whom the findings may be generalized.  
Results would apply to adult patients with moderate to severe abdominal, flank and musculoskeletal pain and headache presenting to the ED.

V. In what care settings might the finding apply, or not apply?  
Emergency department; likely the clinic setting as well.

W. To which clinicians or policy makers might the finding be relevant?  
- ED physicians and pharmacists  
- Family, Internal and Sports Medicine providers  
- P&T; pharmacy departments
SECTION 3: Review of Secondary Literature
[to be completed by the Potential PURL Reviewer]
[to be revised by the Pending PURL Reviewer as needed]

Citation Instructions: For up-to-date citations, use style modified from 
http://www.uptodate.com/home/help/faq/using_UTD/index.html#cite & AMA style. Always use Basow DS on editor & current year as publication 
year.

Example: Auth I. Title of article. {insert author name if given, & search 
terms or title.} In: Basow DS, ed. UpToDate [database online]. Waltham, 
Mass: UpToDate; 2009. Available at: http://www.uptodate.com. {Insert 
date modified if given.} Accesses February 12, 2009. [whatever date 
PPRF reviewer did their search.}

For DynaMed, use the following style: 
Depression: treatment {insert search terms or title}. In: DynaMed 
database online]. Available at http://www.DynamicMedical.com. Last 
updated February 4, 2009. {Insert date modified if given.} Accessed June 
5, 2009. {search date}

A. DynaMed excerpts

B. DynaMed citation/
access date

• Acute low back pain
• Migraine - treatment of acute attack in adults

C. Bottom line recommendation or summary of evidence from DynaMed (1-2 sentences)
• ketorolac 10 mg, 15 mg, and 30 mg IV provide similar degree of pain relief (level 1 [likely reliable] evidence) and may be similar for rescue analgesic use
  o The citation for this statement is this article

D. UpToDate excerpts
Search: flank pain; Article: Diagnosis and acute management of suspected nephrolithiasis in adults
• Study cited using 60 mg of ketorolac = effective
• Study cited using morphine + ketorolac 15 mg = results were that using a combination 
was better than using either agent alone
  o “However, the relatively low dose of ketorolac used (standard dose is 30 mg) 
may have partially accounted for these results.”

Search: acute headache treatment; Article: Tension-type headache in adults: Acute treatment
• Study cited comparing IM ketorolac 60 mg, meperidine 50 + promethazine 25 mg, or NS
  o Ketorolac was most effective treatment

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F. Bottom line recommendation or summary of evidence from UpToDate (1-2 sentences) Recommended as a treatment option for flank pain and headaches – higher doses (15-60 mg) are used.

G. Other excerpts (USPSTF; other guidelines; etc.)
   FDA dosing for ketorolac: Acute pain (moderately severe in patients ≥ 50 kg)
   • IM: 60 mg as a single dose or 30 mg every 6 hours (maximum: 120 mg/day)
   • IV: 30 mg as a single dose or 30 mg every 6 hours (maximum: 120 mg/day)

H. Citations for other excerpts

I. Bottom line recommendation or summary of evidence from Other Sources (1-2 sentences) Doses > 10 mg or ketorolac appear to be common practice.

SECTION 4: Conclusions
[to be completed by the Potential PURL Reviewer]
[to be revised by the Pending PURL Reviewer as needed]

A. Validity: Are the findings scientifically valid? 2

B. If A was coded 4, 5, 6, or 7, please describe the potential bias and how it could affect the study results. Specifically, what is the likely direction in which potential sources of internal bias might affect the results?

C. Relevance: Is the topic relevant to the practice of family medicine and primary care practice, including outpatient, inpatient, obstetrics, emergency and long-term care? Are the patients being studied sufficiently similar to patients cared for in family medicine and primary care in the US such that results can be generalized? 1 (extremely well)

D. If C was coded 4, 5, 6, or 7, please provide an explanation.

E. Practice changing potential: If the findings of the study are both valid and relevant, are they not a currently widely accepted recommendation among family physicians and primary care clinicians for whom the recommendation is relevant to their patient care? Or are the findings likely to be a meaningful variation regarding awareness and acceptance of the recommendation? 1 (definitely a change from current practice)
F. If E was coded as 1, 2, 3, or 4, please describe the potential new practice recommendation. Please be specific about what should be done, the target patient population and the expected benefit. The change in practice would be to use a lower dose IV ketorolac (10 mg) to treat moderate to severe acute pain in the emergency department or clinic setting in adults under the age of 65 without contraindications or precautions to NSAID therapy. The benefit would be decreased risk of bleeding and acute kidney injury that have been associated with the higher doses of ketorolac.

G. Applicability to a Family Medical Care Setting:
Is the change in practice recommendation something that could be done in a medical care setting by a family physician (office, hospital, nursing home, etc.), such as a prescribing a medication, vitamin or herbal remedy; performing or ordering a diagnostic test; performing or referring for a procedure; advising, education or counseling a patient; or creating a system for implementing an intervention? 2

H. If G was coded as a 4, 5, 6, or 7, please explain.

I. Immediacy of Implementation:
Are there major barriers to immediate implementation? Would the cost or the potential for reimbursement prohibit implementation in most family medicine practices? Are there regulatory issues that prohibit implementation? Is the service, device, drug, or other essentials available on the market? 2

J. If I was coded 4, 5, 6, or 7, please explain why.

K. Clinically meaningful outcomes or patient oriented outcomes:
Do the expected benefits outweigh the expected harms? Are the outcomes patient oriented (as opposed to disease oriented)? Are the measured outcomes, if true, clinically meaningful from a patient perspective?
1 (definitely clinically meaningful or patient oriented)

L. If K was coded 4, 5, 6, or 7 please explain why.

M. In your opinion, is this a pending PURL? 2
1. Valid: Strong internal scientific validity; the findings appear to be true.
2. Relevant: Relevant to the practice of family medicine.
3. Practice Changing: There is a specific identifiable new practice recommendation that is applicable to what family physicians do in medical care settings and seems different than current practice.
4. Applicability in medical setting.
5. Immediacy of implementation
N. Comments on your response for question M.
This is a well-designed study with generalizable results. Using lower doses of ketorolac can provide a similar therapeutic response to acute pain while limiting the associated risks. Providers can immediately implement this strategy. May be less applicable to some FM practices that do not administer IV medications.