A comparison of NSAIDs for acute, non-radicular low back pain. A randomized trial

Specific Aims

More than 2.5 million patients present to US emergency departments (ED) annually with low back pain.(1) Up to ½ of ED patients with acute, new onset low back pain (LBP) report persistent moderate or severe pain one week after the ED visit.(2-5) Non-steroidal anti-inflammatory drugs (NSAIDs) are an effective treatment of acute LBP, though their impact is only modest.(6) Combining NSAIDS with oxycodone,(3) skeletal muscle relaxants,(2, 3) or diazepam(5) does not improve outcomes.

Ketorolac is an NSAID that can be used for the management of moderately severe acute pain that requires analgesia at the opioid level; its mechanism of action, similar to other NSAIDs, is not completely understood. (7) There is some literature suggesting that ketorolac may afford faster and superior pain relief when compared to other NSAIDS.(8,9)

Given the poor pain and functional outcomes that persist beyond an ED visit for acute LBP, we propose a clinical trial to determine whether there is a difference in efficacy between the NSAIDs ketorolac, ibuprofen, and diclofenac and for the treatment of acute, non-traumatic, non-radicular low back pain. We will test the following hypothesis:

A daily regimen of ketorolac will provide greater relief of LBP than ibuprofen or diclofenac 5 days after an ED visit, as measured by the Roland Morris Disability Questionnaire.

Overview.
This will be a three armed, double-blind, comparative effectiveness study, in which we enroll patients during an ED visit for musculoskeletal LBP and follow them by telephone two and five days later. Patients will be randomized to receive a 5 day supply of ketorolac, diclofenac, or ibuprofen. Every patient will receive a low back pain education session.

Subject selection.
Our goal is to include in this study a broad representation of patients with musculoskeletal back pain who are likely to respond to the investigational medications and who would not be considered candidates for spinal surgery or targeted epidural intervention. We hope for a widely generalizable study and therefore will not require diagnoses to be contingent on advanced imaging studies.

Inclusion criteria:
-Present to ED primary for management of LBP, defined as pain originating between the lower border of the scapulae and the upper gluteal folds. Flank pain, that is pain originating from tissues lateral to the paraspinal muscles, will not be included.
- Musculoskeletal etiology of low back. Patients with non-musculoskeletal etiologies such as urinary tract infection, ovarian cysts, or influenza like illness will be excluded. The primary clinical diagnosis, at the conclusion of the ED visit, must be a diagnosis consistent with non-traumatic, non-radicular, musculoskeletal LBP.
-Patient is to be discharged home.
- Age 18-64 Enrollment will be limited to adults younger than 65 years because of the increased risk of adverse medication effects in the elderly.
-Non-radicular pain. Patients will be excluded if the pain radiates below the gluteal folds in a radicular pattern.
-Pain duration $\leq$2 weeks (336 hours). Patients with more than two weeks of pain are at increased risk of poor pain and functional outcomes.(10)
-Prior to the acute attack of LBP, back pain cannot occur more frequently than once per month. Patients with more frequent back pain are at increased risk of poor pain and functional outcomes.(10)
-Non-traumatic LBP: no substantial and direct trauma to the back within the previous month
-Functionally impairing back pain: A baseline score of > 5 on the Roland-Morris Disability Questionnaire (Appendix)

Exclusion criteria:
-Not available for follow-up
-Pregnant
-Chronic pain syndrome defined as use of any analgesic medication on a daily or near-daily basis
-Allergic to or intolerant of investigational medications
-Contra-indications to investigational medications: 1) known peptic ulcer disease, chronic dyspepsia, or history of gastrointestinal bleed 2) Severe heart failure (NYHA 2 or worse) 3) Chronic kidney disease (GFR <60ml/min) 4) Current use of anti-coagulants 5) cirrhosis (Child Pugh A or worse) or hepatitis (transaminases 2x the upper limit of normal)

Investigational medication.

A. Ibuprofen 600mg, orally, every 8 hours as needed
B. Diclofenac 50 mg, orally, every 8 hours as needed
C. Ketorolac 10 mg, orally, every 8 hours as needed

In an effort to maximize effectiveness while minimizing side effects, patients will be instructed to take one capsule of the investigational medication every 8 hours as needed for low back pain. All study patients will be given a five day supply of investigational medication.

Outcome measures.

1. Roland Morris LBP Disability Questionnaire (RMDQ)--Reproduced in the Appendix. This 24-item LBP functional scale is recommended for use in LBP research.(11) Its yes/ no format is amenable to telephone follow-up. We have used it successfully to obtain post-ED follow-up in five previous LBP studies involving more than 1500 patients.
2. Ordinal pain scale ("severe", "moderate", "mild", or "none"). Study participants will be asked to describe their worst back pain in the previous 24 hours.
3. Medication requirements: "What medications did you use to treat your low back pain in the previous 24 hours?"
4. Low back pain frequency: "Over the last 24 hours, how often were you in pain? Not at all, Rarely, Sometimes, Usually, Always". Low back pain symptomatology is quite variable. Some patients may experience no pain unless they move a certain way. Others may experience a constant low level of pain. This question will help determine the burdensomeness of the LBP in the patient's daily life.
5. Satisfaction, as measured by response to this question: The next time you go to the ER with low back pain, do you want to get the same combination of medications?

Primary outcome

The change in Roland Morris Disability scale between the baseline ED visit and the five day follow-up (Roland-Morris $_{\text{baseline}}$ - Roland-Morris $_{\text{day 5}}$). The baseline questions will refer to the time period immediately prior to ED presentation (Before you came to the ER today, were you able to…..).

Secondary outcomes

The following outcomes will be assessed 48 hours and 5 days after ED discharge:

1. Worst LBP over the previous 24 hours, using a four point ordinal scale: severe, moderate, mild, or none
2. Frequency of low back pain using the five point Likert scale: Not at all, Rarely, Sometimes, Usually, Always
3. Use of any analgesic or LBP medication within the previous 24 hours.
4. Absolute RMDQ score
5. Day post ED discharge able to return to all usual activities
6. Number of visits to any healthcare provider.
7. Satisfaction with treatment
8. Frequency of adverse events including

   -GI side effects (dyspepsia, nausea, and bleeding)
   -All other side effects

Randomization and blinding

The pharmacist will perform randomization in blocks of 4 based on a sequence generated at http://randomization.com The investigational medication will be masked by placing tablets into identical capsules, which will be packed with scant amounts of lactose and sealed. This masking will take place in a secure location inaccessible to ED personnel. All clinical staff and patients will be blinded. Patients will be presented with one bottle of investigational medication labeled with dosing instructions.

Details of protocol

Prior to discharge from the ED and after the patient's pain has been controlled, the healthcare provider will refer appropriate patients to study personnel for screening. Research associates will ascertain baseline socio-demographic information, low back pain history, and baseline variables discussed above. A urine pregnancy test will be performed. Research personnel will provide each patient with a 15-minute educational intervention. This will be based on NIAMS's Handout on Health: Back Pain information webpage (available at http://www.niams.nih.gov/Health_Info/Back_Pain/default.asp) Research personnel will review each section of the information sheet with the patient and elicit questions. Patients will be discharged with one medication vial, containing a five day supply of ketorolac, diclofenac or ibuprofen. Patients will be cautioned not to take off protocol LBP medication without first consulting with a healthcare provider. Patients will be cautioned not to drink alcohol while using study medications. Patients will be encouraged to follow-up with their primary care physician. Research personnel will use REDCap form to capture data. Follow-up phone calls will be conducted 48 hours, and five days after ED discharge. Follow-up will be attempted daily until successful. For patients difficult to contact, express courier or home visit will be used to obtain follow-up information.

Analysis

An intention-to-treat analysis will be performed among all patients for whom primary outcome data is available. The primary outcome will be a comparison of the change in RMDQ between baseline and day 5. We will look for differences between groups using ANOVA. The mean difference between groups will be reported with 95%CI—if this 95%CI does not cross zero, the result will be considered statistically significant. For patients with missing 5 day follow-up data, we will perform two sensitivity analyses in which we assume universally good outcomes among all patients with missing data in one arm and universally bad arms among those with missing data in the other; we will the reverse these assumptions. Secondary outcomes will be reported as rates with 95%CI. The between group difference will be reported with 95%CI. A per protocol efficacy analysis will be conducted among those patients who use the investigational medication at least once.

Sample size calculation

We based assumptions on a recently completed RCT of LBP treatment.(3) The mean improvement in RMDQ among those who receive an NSAID alone was 10.2. The standard deviation was 8.9. A widely accepted minimum clinically important improvement of 5 points on the RMDQ would require those randomized to active medication to demonstrate a mean improvement of 15.2 on the RMDQ. Using a standard alpha of 0.05 and a beta of 0.20, we determined the need for 60 subjects in each arm. To account for protocol violations and patients lost-to-follow-up (typical lost-to-follow-up rate is 5-10%) and to ensure sufficient power for the per protocol analysis (in our previous ED-based LBP studies, up to 1/3 of enrolled patients have not used the medication more than once), we intend to enroll 66 patients in each arm (total n= 198).

Data Safety Monitoring Committee

This committee will be comprised of Dr. Polly Bijur, PhD, an epidemiologist and Dr. David Esses, MD, the director of the Moses ED. The committee will meet every month with the PI to 1) monitor adverse events and develop strategies to minimize these; and, 2) monitor recruitment and enrollment. There will not be an interim analysis.

Consent

Study personnel will obtain informed consent once the patient's pain has been controlled and the patient is ready for discharge from the ED. The attending physician will assess the patient's capacity to consent to participate in this study.

Risks/Benefits

NSAIDs are commonly used in more than 2.5 million annual US ED visits for LBP. Regardless of results, this study will have a national impact. All study subjects receive an NSAID and thus are likely to benefit. There may be a NSAID that is superior to the others in achieving pain relief. In addition to breach of confidentiality, which is unlikely, and inconvenience to the subject, which will undoubtedly occur, some subjects will possibly experience adverse medication effects. For the most part, these are minor events. Non-steroidals can cause life-threating gastro-intestinal bleeding, but this is unlikely in patients screened for gastro-intestinal illness who will take the medication for one week only. Non-steroidals increase cardiovascular and and risk of renal injury and may worsen blood pressure control.

Data Storage & Confidentiality

Data will be stored and maintained in REDCap. Data analysis will occur on password-protected computers. Consent documents will be maintained in locked research cabinets. Only study personnel will have access to the data and consent documents.

References

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Appendix 1. Roland Morris low back pain disability questionnaire

1.	Over the last 24 hours, I have stayed home most of the time because of my back pain:	No[0]	Yes[1]
2.	Over the last 24 hours, I changed position frequently to try to get my back comfortable:	No[0]	Yes[1]
3.	Over the last 24 hours, I walked more slowly than usual because of my back:	No[0]	Yes[1]
4.	Over the last 24 hours, I have not been doing any jobs that I usually do around the house because of my back pain:	No[0]	Yes[1]
5.	Over the last 24 hours, I used a handrail to get upstairs because of my back pain:	No[0]	Yes[1]
6.	Over the last 24 hours, I lay down to rest more often because of my back pain:	No[0]	Yes[1]
7.	Over the last 24 hours, I have had to hold on to something to get out of an easy chair because of my back pain	No[0]	Yes[1]
8.	Over the last 24 hours, I have tried to get other people to do things for me because of my back pain:	No[0]	Yes[1]
9.	Over the last 24 hours, I got dressed more slowly than usual because of my back pain:	No[0]	Yes[1]
10.	Over the last 24 hours, I only stood up for short periods of time because of my back pain:	No[0]	Yes[1]
11.	Over the last 24 hours, I tried not to bend or kneel down because of my back pain:	No[0]	Yes[1]
12.	Over the last 24 hours, I found it difficult to get out of a chair because of my back pain:	No[0]	Yes[1]
13.	Over the last 24 hours, my back was painful almost all of the time:	No[0]	Yes[1]
14.	Over the last 24 hours, I found it difficult to turn over in bed because of my back pain:	No[0]	Yes[1]
15.	Over the last 24 hours, my appetite was not very good because of my back pain:	No[0]	Yes[1]
16.	Over the last 24 hours, I have had trouble putting on my socks (or stockings) because of the pain in my back or leg:	No[0]	Yes[1]
17.	Over the last 24 hours, I could only walk short distances because of my back pain:	No[0]	Yes[1]
18.	Over the last 24 hours, I slept less well because of my back:	No[0]	Yes[1]
19.	Over the last 24 hours, I got dressed with the help of someone else because of my back pain:	No[0]	Yes[1]
20.	Over the last 24 hours, I sat down for most of the day because of my back:	No[0]	Yes[1]
21.	Over the last 24 hours, I avoided heavy jobs around the house because of my back pain:	No[0]	Yes[1]
22.	Over the last 24 hours, I was more irritable and bad tempered with people than usual because of my back pain,	No[0]	Yes[1]
23.	Over the last 24 hours, I went upstairs more slowly than usual because of my back pain	No[0]	Yes[1]
24.	Over the last 24 hours, I stayed in bed most of the time because of my back pain:	No[0]	Yes[1]