A Randomized Study of Topical Diclofenac versus Oral Ibuprofen for Acute Non-Radicular Low Back Pain

Protocol ID: **2020-12418**
NCT04611529

A randomized study of topical diclofenac versus oral ibuprofen for acute non-radicular low back pain

In industrialized nations such as the United states, low back pain carries a lifetime prevalence of over 80% and results in an aggregate 2.7 million annual visits to US emergency departments. (1,2) RCT's comparing NSAIDS to placebo support the use of this medication as first-line treatment in patients with acute low back pain without sciatica. (3) Despite this, the magnitude of NSAID effectiveness remains small, leading patients with low back pain to report persistent pain, analgesic use, and functional impairment after an ED discharge. (3,4) Furthermore, the addition of other pharmacologic treatments such as oxycodone, muscle relaxants, and benzodiazepines have not improved outcomes when added to NSAIDS. (5,6) Topical NSAIDS, such as diclofenac, are effective in the treatment of musculoskeletal pain but have not been studied specifically in patients with low back pain. (9)

The current literature reveals that topical NSAIDS may achieve similar therapeutic effects with fewer systemic side effects when compared to oral NSAIDS. For example, an in vivo study comparing oral vs topical ibuprofen showed similar concentration of the drug in muscle tissue yet a 300-fold lower plasma concentration for patients receiving topical ibuprofen. (7) Multiple studies showed a statistically significant reduction in pain when topical diclofenac was compared to placebo in patients with musculoskeletal sports injuries. (8) Similarly, when used in patients with chronic musculoskeletal pain, topical diclofenac led to a significant reduction in pain after 2 to 4 weeks and no statistical difference when compared to oral diclofenac. (9) When used specifically for patients with acute back pain, a single study was carried out and showed promising results for the diclofenac patch, but this was open-label, uncontrolled, and generally of poor quality. (10)

Given the poor pain and functional outcomes that persist beyond an ED visit for acute musculoskeletal low back pain, we propose a clinical trial to test the following three hypotheses:

1) Combining topical diclofenac gel with oral ibuprofen will result in better LBP functional outcomes than oral ibuprofen + placebo gel, as measured by improvement in the Roland Morris Disability Questionnaire 2 days after ED discharge
2) Combining topical diclofenac gel with oral ibuprofen will result in better LBP functional outcomes than diclofenac gel + oral placebo, as measured by improvement in the Roland Morris Disability Questionnaire 2 days after ED discharge
3) Topical diclofenac + oral placebo and topical placebo + oral ibuprofen will result in comparable LBP functional outcomes, as measured by improvement in the Roland Morris Disability Questionnaire 2 days after ED discharge

Overview

This will be a double-blind, placebo-controlled comparative effectiveness trial in which we enroll patients during an ED visit for musculoskeletal LBP and follow them by telephone two and seven days later. Patients will be randomized into one of three separate treatment groups: topical diclofenac gel + oral ibuprofen, topical diclofenac gel + placebo oral medication, oral ibuprofen + placebo gel. All patients will receive a 2-day supply of investigational medication.

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 18-69 Enrollment will be limited to adults younger than 70 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 must occur less 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

-Any analgesic medication use on a daily or near-daily basis

-Allergic to or intolerant of investigational medications

-Open wounds or skin breakdown of the lower back

-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 400mg orally + Diclofenac 1% gel, 4g topically, every 6 hours as needed
B. Ibuprofen 400mg orally + placebo gel topically, every 6 hours as needed
C. Diclofenac 1% gel, 4g topically + placebo capsules, orally, every 6 hours as needed

Participants will be instructed to take one capsule of the investigational medication and apply the investigational gel together every 6 hours as needed for the pain. All study patients will be given a two-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 two-day follow-up (Roland-Morris baseline - Roland-Morris day 2). 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 2 days and 7 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. 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)
   -application site skin reactions such as dermatitis
   -All other side effects

Randomization and blinding

The pharmacist will perform randomization in blocks of 6 based on a sequence generated at http://randomization.com The investigational oral medication will be masked by placing tablets into identical capsules, which will be packed with scant amounts of lactose and sealed. The investigational topical medication will be masked by placing gel into an unidentified tube. 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 vial and one tube 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. Research personnel will provide each patient with a 10-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 two-day supply of ibuprofen or placebo and one tube containing a two-day supply of diclofenac gel or placebo gel. Additionally, the patients will be provided with a measuring tape and instructed to measure a 4.5-inch length of gel corresponding to a dose of 4 g of the investigational topical medication for each application. Patients will be instructed to use both the oral and topical medication together if they have pain. Patients will be cautioned not to take off protocol LBP medication without first consulting with a healthcare provider. 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 seven 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.

Sample size calculation

We based assumptions on a recently completed RCT of LBP treatment. (11) 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).

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 2. The mean difference between groups will be reported with 95%CI. For the superiority analyses, if the 95%CI does not cross zero, the result will be considered statistically significant. For the equivalence analysis, if the 95%CI does not cross 5 or -5, the result will be considered statistically significant. For patients with missing 2 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 then 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.

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. 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 two days only. Non-steroidals increase cardiovascular and risk of renal injury and may worsen blood pressure control. When used topically, non-steroidals may cause application site reactions, including dermatitis.

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.

Unblinding
Subject treatment assignments will remain blinded until the final subject has completed follow up and all data has been recorded and validated. Urgent, immediate unblinding due to medical emergency may be authorized by the Investigator.

1. Golob A, Wipf J. Low Back Pain. Med Clin N Am 98 (2014) 405–428
2. Friedman BW, Chilstrom M, Bijur PE, Gallagher EJ. Diagnostic Testing and Treatment of Low Back Pain in United States Emergency Departments. SPINE Vol. 35, No. 24, pp E1406–E1411, 2010
3. Roelofs PD, Deyo RA, Koes BW, Scholten RJ, van Tulder MW**.** Nonsteroidal anti-inflammatory drugs for low back pain: an updated Cochrane review. Spine. 2008;33(16):1766-74.
4. Friedman BW, O'Mahony S, Mulvey L, Davitt M, Choi H, Xia S, et al. One-week and 3-month outcomes after an emergency department visit for undifferentiated musculoskeletal low back pain. Annals of emergency medicine. 2012;59(2):128-33 e3.
5. Friedman BW, Dym AA, Davitt M, Holden L, Solorzano C, Esses D, et al. Naproxen With Cyclobenzaprine, Oxycodone/Acetaminophen, or Placebo for Treating Acute Low Back Pain: A Randomized Clinical Trial. JAMA. 2015;314(15):1572-80.
6. Friedman BW, Irizarry E, Solorzano C, Khankhel N, Zapata J, Zias E, et al. Diazepam is no better than placebo when added to naproxen for acute low back pain. Ann Emerg Med. 2017 Aug;70(2):169-176
7. Tegeder I, et al. Application of microdialysis for the determination of muscle and subcutaneous tissue concentrations after oral and topical ibuprofen administration. Clin Pharmacol Ther. 1999 Apr;65(4):357-68.
8. McCarberg B, D'Arcy. Options in topical therapies in the management of patients with acute pain. Postgrad Med. 2013 Jul;125(4 Suppl 1):19-24.
9. Shinde VA, et al. Efficacy and Safety of Oral Diclofenac Sustained release Versus Transdermal Diclofenac Patch in Chronic Musculoskeletal Pain: A Randomized, Open Label Trial. J Pharmacol Pharmacother. 2017 Oct-Dec;8(4):166-171. doi: 10.4103/jpp.JPP_35_17.
10. Gimbel J, Jacobs D, Pixton G, Paterson C. Effectiveness and safety of diclofenac epolamine topical patch 1.3% for the treatment of acute pain due to back strain: an open-label, uncontrolled study. Phys Sportsmed. 2011 Feb;39(1):11-8. doi: 10.3810/psm.2011.02.1857
11. Friedman BW, Dym AA, Davitt M, Holden L, Solorzano C, Esses D, et al. Naproxen With Cyclobenzaprine, Oxycodone/Acetaminophen, or Placebo for Treating Acute Low Back Pain: A Randomized Clinical Trial. JAMA. 2015;314(15):1572-80.

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]