Efficacy of Lidocaine Patch in Acute Musculoskeletal Pain in the Emergency Department: A Prospective Randomized Controlled Study.

NCT03571737

April 12, 2018

Protocol

Title: Efficacy of Lidocaine Patch in Acute Musculoskeletal Pain in the Emergency Department: A Prospective Randomized Controlled Study.

Background and introduction:

In 2014, musculoskeletal injuries accounted for about 10% of the emergency department visits in the nation for the year. [8] Analgesics comprise 30% of the prescriptions mentioned in the emergency department, comprising of both over-the-counter options as well as prescriptions. [8] These analgesics alleviate the acute phase of pain while patients adhere to the standard treatment of RICE: Rest, Ice, Compression, Elevation of the affected site. NSAIDs and acetaminophen comprise of the first-line analgesic treatment for mild to moderate pain, with NSAIDs being theorized to decrease the inflammatory response that comes with acute injury and to alleviate the swelling. [13] One study examining ankle sprains showed that more than half of the pain was alleviated twice as much with the ibuprofen group versus a conservative treatment without medications group. [15] Ibuprofen and other NSAIDs have been approved for mild to moderate pain, along with osteoarthritis, rheumatoid arthritis, antipyretic, dysmenorrhea. Frequently, if pain is not controlled with acetaminophen or NSAIDs, a different modality of pain control may need to be added. In the past opioid medications were given for unrelieved pain but given the recent concern for addiction to these medications, alternative therapies for pain control are being studied intensively. [5]

Topical lidocaine patches are an alternative therapy that has been FDA-approved for the treatment of post-herpetic neuralgia. [3,6] In addition, they have also been used off-label for other pain conditions, such as osteoarthritis, exacerbation of chronic back pain, rib fractures, incision-related pains, etc [1,2,7]. Studies have described enhanced relief of pain via combination of analgesics with different mechanisms of actions. Lidocaine may provide a different mechanism of action by using selective inhibition of voltage-gated sodium channels, affecting the A and C fibers, which are main fibers used for nociceptors for pain responses.[9] Due to the topical nature of the medications, side effect profiles are more favorable versus the systemic absorptions. [3] This may be advantageous especially in elderly patients who are already burdened with multiple drug interactions and delirium. Prior studies using the lidocaine 5% transdermal patch have shown an onset of action as early as 30 minutes (peak benefit 4-12 hours) with associated reduction in pain intensity.[10] Lidocaine has also been seen to improve pain within a longer time frame post-administration. [14] Given the lidocaine patch has recently been turned into an over-the-counter medication, it would be beneficial to further investigate the efficacy and possibility of its use in patients presenting with acute musculoskeletal pain in the Emergency Department. In this study, we will be performing the study using the over-the-counter formulation of lidocaine 4% patch (Lidocare Pain Relief Patch ™), which compared to 5% formulation, may provide less of the

harmful side effects with non-inferior efficacy. [12] (These side effects may include cardiac arrest, CNS depression, unintentional overdose, in addition to those listed in the exclusion criteria).

Hypothesis:

Treatment of patients who visit the emergency department with acute musculoskeletal pain with lidocaine patch plus an NSAID (ibuprofen in the study) will provide significant improvement in pain scores and decrease return visits versus treatment with only ibuprofen

Study objectives:

Primary objective: To determine if adding lidocaine patch to treatment with NSAIDs (ibuprofen in the study) will significantly improve patients' pain scores from acute musculoskeletal injuries

Secondary objective:

To examine rate of return visit to the emergency department for acute musculoskeletal pain, given paucity of data on the subject.

To demonstrate that lidocaine patch plus ibuprofen will decrease return visits for additional pain medications versus patients treated with only ibuprofen for acute musculoskeletal pain

Study design:

Prospective, Open-label, randomized controlled trial

Inclusion criteria:

Age ≥ 18 years old

English-speaking patients

Chief complaint of musculoskeletal pain lasting ≤7 days

Area of greatest pain isolated to one body part

No prior ED visits recorded on electronic medical records for the chief complaint

Exclusion criteria:

Age < 18 years old

Pregnant/Breastfeeding patients

Non-English-speaking population

Multiple traumatic injuries or injury requiring consultation with the trauma service per hospital guidelines

Cellulitis/infection overlying the injuries

Open wound overlying the injuries

Pain caused by penetrating injury

Absolute contraindications to medications, including anaphylaxis to lidocaine or NSAIDs, history of active GI bleeding or recent CABG surgery precluding NSAIDs, severe hepatic disease (hepatitis, cirrhosis in current chart or prior history or elevation in liver function tests to clinically significant levels in past 6 months), severe kidney disease (Cr clearance <30 mL or history of CKD stage 3 or worse), congestive heart failure.

Medication contraindications (from FDA website) - concurrent use of medications below:

- Alcuronium
- Amphotericin B
- Amprenavir
- Atracurium
- Cimetidine
- Edrophonium
- Enflurane
- Fosphenytoin
- Halothane
- Nadolol
- Oxprenolol
- Pentazocine
- Propafenone

Patients on class I antiarrhythmics therapy (including lidocaine, procainamide, disopyramide etc)

Injuries requiring splint/casting where patient may not be able to reach the area of greatest pain to apply and reapply the patch

Prior history of chronic pain in the affected area (defined as ≥ 6 weeks of pain)

Patients who received opioid medication in triage area or within 4 hours of initial treatment

Inability to give pain scores due to mental status (including intoxications, hallucinations, psychosis, profound mental disability prohibiting patient from giving clear medical history)

Initial numerical pain scale score of 0 (which would constitute “no pain” on the scale)

Requiring opiate medication or muscle relaxants (Flexeril, Valium, Tizanidine, Robaxin etc) during the initial visit to ED at the discretion of the provider.

Patients who received < 800 mg oral dosage of ibuprofen in triage

Patient Identification:

Patients will be identified at ED triage with chief complaint related to acute (≤7 days duration) isolated musculoskeletal pain.

Sample size:

Differences in pain scores will be analyzed using a one-tail t-test. With an a priori power analysis, we would like to see at least a 2-point difference in pain score [11], with minimally clinically significant difference of 1.3 points. To achieve this, we will need at least 140 patients total (70 in each arm). Alpha will be set at 0.05, with power of 90%. Allowing for error or patient dropping out, we request that 180 people be enrolled in the study. At Vidant Medical Center, at least 682 patients in the month of March 2018 have come into the ED that werebilled as having complaint of musculoskeletal pains.

Timeline:

Patients will be identified at ED triage with chief complaint related to acute (≤7 days duration) of isolated musculoskeletal pain of one area of body. Given the volume and rate of visit through the Vidant Medical Center, the patient enrollment may require only a few month's time.

At the time of identification, inclusion and exclusion criteria will be reviewed via EHR. If unable to discern inclusion and exclusion criteria via this method, patient may be verbally asked about these criteria prior to obtaining consent. A full medical evaluation will be performed as is done in all ED patients prior to initiation of any study activities.

Written consent will be obtained in triage at that time about this study, after explaining benefits and risks to each participant.

Patients will be asked at the time an initial pain level with Numerical Pain Rating Scale, which will provide with a number from 0-10, with 0 being no pain, 10 being the worst pain possible.

Patients will then be given one PO ibuprofen 800mg, which may be either in triage or at the room pending the flow of the emergency department.

Providers will have option of two different envelopes with treatment options, which the choice of envelope will be randomized. One arm will be treatment with lidocaine patch (Lidocare Pain Relief Patch ™ (containing lidocaine 4%) patch) and ibuprofen (PO 800mg). The other arm will be the control arm, where only ibuprofen (PO 800mg) will be prescribed. The lidocaine patch will be applied to the area of maximal pain and will be replaced daily per the prescription (applied to the area up to 12 hours for each time then removed for 12 hours before reapplication). Lidocaine patches will be kept in the ED pyxis and dispensed by study team.

Provider will give the assigned treatment from the envelope. If the patient was randomized to the control arm, patient will not be receiving any further NSAIDs in the treatment rooms if initial dosing was at triage.

30 min after intervention (ibuprofen only or lidocaine patch plus ibuprofen) and at discharge, patient will be asked to repeat the pain scale. This will be appropriate timing, since the ibuprofen's onset of action is published as 25 minutes with a duration of action from 4-6 hours. No published time to effect data for 4% lidocaine patches can be found. It is noted to be variable based on vascularity of site of placement. However, the use of 4% lidocaine topical cream is noted to be effective within 5-20 minutes. In addition, measures of blood levels of lidocaine show that levels peak at 6-8 hours after application of a 4% patch. Because of the mechanism of action of lidocaine patches is to reduce the firing of pain fibers directly beneath the patch, it is generally considered a "fast-acting" approach to pain relief. Studies looking at 5% lidocaine patch has also noted some improvement to pain within 30 minutes as noted in background section. We believe that 30 minutes is sufficient for a patient to experience some relief of pain after patch application.

Patients will be supplied for 3 days' worth of lidocaine patches to be applied every 12 hours each day with removal in 12 hours, along with prescription of 3 days of ibuprofen 800mg PO every 8 hours. Patients who are randomized into the ibuprofen only arm will get prescription for at 3 days' supply of ibuprofen only with the same 800mg PO every 8 hours.

Prior to discharge, patient will be asked to repeat the pain scale, with the timing of this pain scale also noted at this time.

We will review the patient's electronic chart and see if there was a repeat visit to either Vidant ED or Vidant/ECU primary care provider (who are connected via Vidant's EPIC EHR system) within 1 week for same chief complaint. If available, we will also review the numerical analog scale at the visit.

The patient will also be contacted via phone to obtain a final pain score within 48 - 72 hours of discharge. At that time, a survey/questionnaire about the phone call would obtain information about the final pain scale score, medication usage/compliance, and any rescue prescriptions obtained after the initial visit. If patient's primary care provider was unable to be viewed on the EHR, we would also ask about any follow-up visit that has been done or planned within 1 week of initial visit for the same complaint.

It is anticipated (based on experience) that if a patient has not achieved pain relief they will return, or visit a primary care physician within 48 hours. The follow up time frame is based on the fact that the patients are provided with 72 hours of pain control. If the pain returns at that time, or they did not achieve relief, they are expected to seek medical care in the ED or elsewhere. The study will be performed as an Intention to Treat study, meaning that if follow up

data is not available for any patient, they will be noted as a treatment failure so that results are not overstated in the face of low follow-up.

Risks and Benefits:

Both are medications, which intrinsically carry the risks of adverse effects. However, given that both of the medications are available over-the-counter for pain relief without necessitating the evaluation of a qualified medical personnel, the risks listed below would be a very infrequent happening. Other risks not listed below with the manufacturer's label are listed above in the exclusion criteria.

Lidocare 4% Pain Relief Patch**:**

Benefit: For the temporary relief of pain.

Risks per Manufacturer: For external use only.

Do not use on large areas of the body or on cut, irritated skin on open wounds or sensitive skin for more than one week without consulting a doctor. Do not use if you are allergic to lidocaine or any of the inactive ingredients listed (Crospovidone, menthoxypropanediol, non-woven backing fabric, polyester film, non-latex rubber based adhesive, vanillyl butyl ether)

Do not allow contact with eyes. Rash, itching or skin irritation develops. Symptoms persist for more than 7 days or clear up and occur again within a few days.

Advil, Motrin, Ibuprofen:

Benefit: For temporary relief of pain

Risks per Manufacturer:

Reported side effects were higher at doses of 3200 mg/day than at doses of 2400 mg or less per day in clinical trials of patients with rheumatoid arthritis.

GASTROINTESTINAL: Nausea, epigastric pain, heartburn, diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract (bloating and flatulence) Gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, melena, gastritis, hepatitis, jaundice, abnormal liver function tests; pancreatitis

CENTRAL NERVOUS SYSTEM: Dizziness, headache, nervousness, Depression, insomnia, confusion, emotional liability, somnolence, aseptic meningitis with fever and coma, Paresthesias, hallucinations, dream abnormalities, pseudotumor cerebri

DERMATOLOGIC: Rash, (including maculopapular type), pruritus, Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia, Toxic epidermal necrolysis, photoallergic skin reactions

SPECIAL SENSES: Tinnitus, Hearing loss, amblyopia (blurred and/or diminished vision, scotomata and/or changes in color vision), Conjunctivitis, diplopia, optic neuritis, cataracts

HEMATOLOGIC: Neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coombs positive), thrombocytopenia with or without purpura, eosinophilia, decreases in hemoglobin and hematocrit, Bleeding episodes (eg epistaxis, menorrhagia)

METABOLIC/ENDOCRINE: Decreased appetite, Gynecomastia, hypoglycemic reaction, acidosis

CARDIOVASCULAR: Edema, fluid retention (generally responds promptly to drug discontinuation) (see Congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations Arrhythmias (sinus tachycardia, sinus bradycardia)

ALLERGIC: Syndrome of abdominal pain, fever, chills, nausea and vomiting; anaphylaxis; bronchospasm, Serum sickness, lupus erythematosus syndrome. Henoch-Schonlein vasculitis,angioedema

RENAL: Acute renal failure, decreased creatinine clearance, polyuria, azotemia, cystitis, Hematuria, Renal papillary necrosis

MISCELLANEOUS: Dry eyes and mouth, gingival ulcer, rhinitis

Ethics:

Patient may potentially benefit by receiving additional treatment for their pain. Patients who are randomized to the NSAIDs only arm will still be receiving standard of care for their pain. There is minimal harm given to patients, given that topical preparation limits systemic absorption. We will also screen out those who have contraindication to any of the two medications in the study. Written consent will be obtained. Risks and benefits will be explained at the time of consent. There will not be any coercion or financial incentive to enroll in the study. The staff will be adhering to HIPAA to maintain privacy and confidentiality. Patients will be randomized into two treatment arms, and physician providing care will randomize into two treatments. If the patient is requiring more treatment due to an adverse event, physician will freely be able to treat the patient based on physician's discretion. The study team does not have financial ties with the Lidocare company.

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