Arnica and the Management of Pain in Acute Musculoskeletal Extremity Injuries

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1. Study Team

Principal Investigator: Manu Madhok, MD, MPH
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2. Project Title

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3. Introduction

Background/Significance

The Emergency Department (ED) at Children's Minnesota is a Trauma 1 Center which takes care of our state's most severely injured children. However, the majority of traumas it sees are not severely injured but patients with minor to moderate injuries. These patients enter the ED scared and in pain with concerned parents. Our institution's "Children's Comfort Promise" initiative advocates effectively using institutional guidelines and evidence-based research to control the pain all our patients feel during and following their visit.

Pain management in Emergency Department is a key marker for quality of care and the focus is on providing it in a safe, effective and timely manner (Guidelines by Emergency Medical Services, online access). However, there is no standard of care for the management of acute musculoskeletal injury in children (Ali 2010). Currently, ibuprofen is a favorable choice for the treatment of acute musculoskeletal injury pain. Yet studies have shown concern for delayed healing activity associated with NSAIDs like Ibuprofen (Boursinos 2009).

In current practice, we do not offer alternative medications. Homeopathic Arnica Montana is a well-established complimentary medicine and may provide a good alternative for managing acute pain from musculoskeletal injuries, especially in children, given the palatability and rarity of side effects. Extracted from the herb native to the Swiss Alps and the Rocky Mountains, it is commonly used as a topical treatment or an ingestible tablet, but is also found in many mainstream foods, shampoos, and cosmetics (Kouzi 2007).

In adult patients, homeopathic Arnica has been used and studied for it analgesic and anti-inflammatory effects in many surgical settings with mixed results. Placebo-controlled, randomized, double-blinded studies trying to control post-procedural ecchymosis (Kotlus 2010) and pain (Paris 2008) have shown no efficacy of Arnica treatments. Another study focusing on face-lift surgery showed a statistically significant improvement in post-procedural bruising, but did not demonstrate any improvement in how the patient felt post-operatively (Seeley 2006). Some studies, such as a study conducted on 190 patients who underwent a tonsillectomy, have shown statistically significant decreases in post-operative pain scores (Robertson 2007) as a result of Arnica treatments. Another study which looked at swelling after knee surgery showed a statistically significant decrease in knee circumference after taking Arnica post-operatively as compared with placebo (Brinkhaus 2006). Most of the studies were done in adults patients. The effect of Arnica in children with acute musculoskeletal injury is not well studied and needs to be addressed.

Research Question
To compare usual care vs. usual care plus Arnica 1M* (oral) or the placebo for management of pain in acute musculoskeletal extremity injuries. The primary outcome is to determine if subjects use less ibuprofen when given Arnica 1M.

Secondary objective:
To determine if Arnica 1M provides better improvement of pain score
To determine if Arnica 1M provides better relief of swelling

*The concentration of Arnica in a 1M potency remedy is 1 part Arnica in 10^{1000} parts water (Kayne 2006).

4. Study Design and Methodology

Hypothesis
Subjects use less ibuprofen when given Arnica 1M (oral) plus usual care than given placebo plus usual care.

Overview/Scope

Study Design
This is a randomized, double-blind, placebo-controlled clinical trial.

Time Frame/Duration
- During the month following IRB approval, the study team will begin training research assistants on the study procedures. The PI will attend ED nursing huddles and physician and nurse practitioner staff meetings to introduce the study, describe the procedures each groups is expected to complete, and answer questions.
- Once training is complete, enrollment will begin. Active enrollment will take place in the Saint Paul and Minneapolis ED. We anticipate enrollment to take two years.
- Following enrollment, the data will be analyzed and prepared for publication over four months.

Analysis

Sample Size
A sample of 324 patients (162 assign to the arnica plus usual care group and 162 assigned to the placebo plus usual care group) has 80% power to detect a 1 dose reduction of ibuprofen in the arnica group compared to the placebo group using a two sample t-test at the 5% significance level.

The power calculation assumes a clinically relevant reduction of 20% total ibuprofen dosage and published literature on ibuprofen use in pediatric patients following an arm fracture. Drendel et al (2009) showed that patients took 5 doses of ibuprofen on average with a standard deviation of 3.2 doses in the first 72 hours after discharge from the emergency department. A 20% reduction corresponds to a reduction of 1 dose on average.

Analytic Approach
A linear mixed model with the dose reduction of ibuprofen as the dependent variable and, time of Arnica/placebo taken, time of ibuprofen taken and dosage, and Arnica 1M (oral) or placebo group as the predictors will be used to analyze the data to determine if Arnica 1M (oral) provides better

pain relief than placebo in conjunction with standard of care medications. Since participants will be repeatedly measured repeated effect will be used to model the possible correlation of the residual errors within each participant.

A two-sided p-value < 0.05 will be used for significance. All analysis will be completed using SPSS V23.0 (SPSS Inc., Chicago, IL).

5. Subjects

Subjects

162 Subjects in each group, control and experimental, will be required to complete the protocol through follow-up. At least 324 total subjects will be enrolled and randomized in this study.

Recruitment

1. A trained research assistant will identify patients with extremity injuries and approach the treating physician to check eligibility criteria.
2. The research assistant will approach each patient meeting the inclusion criteria. Study goals and objectives will be shared with the patient and parents. Study concepts that are often difficult to understand, such as randomization and blinding, follow-up and data collection, will be explained to the participants and the research staff will allot time for questions.
3. After this process, consent, assent, and HIPAA authorization will be obtained. Patient and parent will be educated on assessment of pain, record medication daily diary and use homeopathic medication. (Appendix 1. Parent Take Home Table, Appendix 2. Instructions for use of homeopathic remedies, Appendix 3. What is Homeopathy)
4. The treating physician will be informed and will place orders for the study medication. The first dose of study medication or placebo will be administered at ED (Appendix4. Parent Handout). The ED physician/nurse practitioner will discharge patients with current standard instructions for soft tissue injuries.
5. A $10 reimbursement of either a Target gift card that will be mailed or a Clincard will be loaded at the completion of the study to compensate for their time in providing needed data during telephone follow-up.

Enrollment

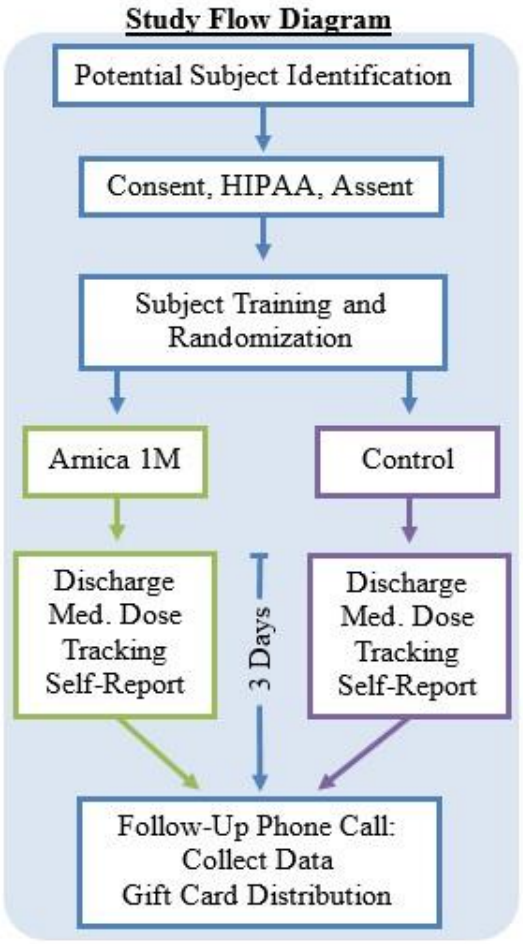
Inclusion Criteria

- Patient's age is between 11 years and 18 years
- Patient presents to the Department with an acute, soft tissue ankle or forearm injury
- Patient has noticeable swelling or bruising at the site of injury
- Patient's initial recorded pain score of 4 or higher on a pain scale of 1 to 10
- Patient's and family's willingness to participate in telephone follow-up

Exclusion Criteria

- Patient is diagnosed with a fracture, either in the ED or upon review by radiology.
- Patient has an allergy to ibuprofen
- Patient is already on a NSAID, acetaminophen, anticoagulant or oral corticosteroid therapy for chronic pain treatment (a NSAID given in triage or use for the current injury is allowed).
- Use of other concurrent complementary medicine therapy, e.g. massage, acupuncture, physical therapy

- Patient has been treated for this injury in the past
- Patient has a bleeding/bruising disorder
- Patient is pregnant or is lactating.
- Patient has a liver or kidney disease, malignancy, infection, immunodeficiency or metabolic syndrome
- Patient is allergic to the *Asteraceae* family of plants (arnica, ragweed, chrysanthemum, marigold, or daisy are the most common)
- Patient is nonverbal, and thus unable to give a pain score
- Patient does not have a working telephone
- Family requires foreign language interpreter during their ED visit.



6. Study Procedures

The graphic to the left details the step-wise flow of the study from enrollment to completion for each patient.

1. During the ED visit

The Emergency Department provider will provide standard of care treatment. The potential patients will be identified and approached. Consent, assent, and HIPAA authorization will be obtained.

After consenting, the patient will be randomized to Arnica or Placebo in conjunction with standard treatment of ibuprofen. Randomization will be conducted by the inpatient pharmacy in a fashion which ensures both the investigators and subjects are blinded to the intervention group.

The study drug will either be the Arnica 1M (oral) or placebo. The Arnica 1M oral pill will be a sucrose sugar pill, which is medicated with the Arnica 1M liquid. The placebo used will be an un-medicated sugar pill. Each dose is two pills.

The Arnica 1M solution will be purchased through Helios Homeopathy Ltd., which is based in the United Kingdom, and will be received, stored, and distributed by the Children's Inpatient Pharmacy. Doses will arrive in bulk, and be separated into vials with 10 pills (i.e., 4 doses and 1 extra dose in case pills are accidently dropped while dispensing from the vial).

The study drug will be ordered by the attending ED provider. Pharmacy will use a pre-determined randomization table to randomize and fill the order. They will send the vial containing the study medication. The ED research assistant will pick up the study drug vial and counsel the family, then will guide and observe the self-administration of the first dose of medication.

The patient's pain score at the time of study enrollment will be collected from the patient, and highest pain score during the ED visit will be collected from the EMR. After the pain score is assessed in the ED, the RA will measure and record the width of both the uninjured and the bruised joint (ankle or wrist) using a paper measuring tape that is used in ED. Simultaneously, the RA will show the parent/guardian how to measure the injured joint.

2. After discharge, follow-up call

Each subject will be given a study sheet (Appendix 1) on which they can record their pain score once per day in the morning after wake up for 3 days which will include a VAS. It will help track how many doses of Arnica the patient took, as well as how many doses of ibuprofen the patient took. It will allow the family to track if the joint was iced or immobilized. This information will be collected during the follow-up phone call.

At home, on day 1, 2, and 3, the parent/guardian will repeat the measurement on the injured joint and record the value on the study sheet. This data will be collected during the follow-up call.

In addition to the data mentioned above, the study team will ask the parent/guardian if the subject has had any loss of function due to the injury, had returned to full activity following the injury, had any missed school or summer activities, if the parent/guardian missed work due to the injury, or if the family returned to the ED or to another medical facility due to the injury. The RA will ask the parent if the patient experienced any side effects, specifically rash, abdominal pain, nausea, vomiting, or fatigue and will ask if they experienced any other effect.

Parent that signs the consent will be the only one designated to track all info required.

<u>Data Requirements</u>

1. Following consent, MRN, date of visit, patient's full name, parent/guardian's first and last name, mailing address, phone number will be collected from the parent.
2. Demographic information including patient's race, ethnicity, date of birth and gender will be collected from the medical record.
3. During ED visit and the follow-up calls, all research questions will be answered by parent/guardian. Data elements include:

- Site of injury
- Pain score
- Swelling measurement in ED
- If bruising was present at onset, how it has changed over day 1, 2 and 3.
- If splint applied
- If ice applied during ED visit
- Medication prescribed by ED provider
- If the patient take all 4 doses of the study medication
- Pain score in day 1, 2 and 3
- If the patient takes ibuprofen, and dose in day 1, 2 and 3
- If the patient seeks health care since the ED visit

- How many days of school and/or activities the patient missed
- How many days of school, work the family members missed
- How many days has the family's usual routine been changed or disrupted
- If the patients experienced: rash, abdominal pain, nausea, vomiting, fatigue
- If topical treatments were used, and what kind

Data will be acquired from the patient and family member/ guardian as well as the treating provider and the electronic medical record (EMR). Appendix 5 describes the data elements captured for this study.

Data will reside in a customized REDCap database residing on the Children's secure network (Appendix 5). Data obtained from the medical record will be immediately added to the secure database. All data from the patient and family, both in the ED and during the telephone follow-up call, will be recorded on a paper data collection sheet and then transferred into the REDCap database.

Visit Schedule

1. During the ED visit

The potential patients will be identified and approached. Consent, assent, and HIPAA authorization will be obtained.

Other research relevant info will be collected during patients' visit in ED. Patients will be trained in using the study sheet (Appendix 1), and measuring swelling.

2. After discharge, follow-up call

One follow-up call will be made during day 4-6 after discharge. The information that patient recorded on study sheet will be collected during the follow-up phone call.

Drug/Device, Handing, Storage (If Applicable)

Homeopathic remedies are prepared by serial dilution and succussion of a "mother tincture". The mother tincture is composed of the herbal material, in this case Arnica Montana, and water or alcohol (Kayne, 2006).

To prepare a 1M Arnica remedy, one drop of the Arnica mother tincture is added to 99 drops of highly purified water in a clean glass vial. The vial is vigorously shaken while striking the vial on a hard surface. This shaking process is known as succussion (Kayne, 2006). The resulting mixture has a potency of 1c. The 1c solution is then emptied from the vial, leaving residual droplets. 99 drops of water are then added to the vial and again succussed to produce a mixture potency of 2c. Each time the solution is diluted and succussed the potency of the mixture increases while the concentration of Arnica decreases. This process is repeated 1000 times to reach a potency of 1000c or 1M. The concentration of Arnica in a 1M potency remedy is 1 part Arnica in 10^{2000} parts water (Kayne, 2006). Several hypotheses have been put forward to explain the potentisation phenomenon cause by succussion, but homeopaths agree that the process of dilution and succussion preserve the therapeutic effect of the original substance while removing the negative side effects, making each homeopathic treatment, ideally, safe and effective (Bellavite 2002, Kayne, 2006).

For patients in the Arnica group, this remedy is loaded onto the sucrose pellets by placing 1-3 drops of Arnica 1M in each vial and shaking the vial to coat the pellets. Each four dose vial will contain 8 sucrose pellets, and an additional 2 pellets in case some are dropped.

Each patient will take the first dose in the ED and take additional doses of the provided medication (Arnica or placebo) every 4 waking hours. After 24 hours, any untaken doses should be discarded. If additional pain control is needed, patients should take ibuprofen as needed.

Topical Arnica remedies, which could be applied directly to the injury site, were an alternative treatment option. The study team elected to use oral medications as the previous studies which showed efficacy used Arnica taken orally (Seeley 2006, Robertson 2007, Brinkhaus 2006).

Patient Withdrawal, Completion, Death

In the case of adverse events requiring medical attention, the subject and family will be un-blinded. If the subject is un-blinded prior to completing the study, they will be withdrawn from the study.

If the subject needs to be un-blinded for any reason, authorization may be given by PI Dr. Manu Madhok. Authorization may be written or verbal. The unblinding procedure is in risks/benefits section.

Patients who have any of the contraindicated conditions listed in the Risks section will be excluded from the study.

7. Risks/Benefits

Potential Risks

Arnica usage is contraindicated in patients who have an allergy to the *Asteraceae* family of plants as well as in patients who are pregnant or lactating, who have an existing liver or kidney disease, bleeding or bruising disorder, malignancy, infection, immunodeficiency or metabolic syndrome.

Arnica should not be used in conjunction with any other homeopathic remedies or treatments. Ingestion of large doses of herbal preparations of Arnica Montana may lead to gastroenteritis or internal bleeding (Kouzi, 2007) although none of the randomized, placebo controlled studies reported a single instance either of these complications (Brinkhaus 2006, Seeley 2006, Robertson 2007, Paris 2008, Kotlus 2010) likely due to low doses of the extracted tincture.

Because data will be collected from patient records, there is a risk for breach of confidentiality.

Methods to Minimize Risks

Our study uses low dose Arnica 1M which is a 1 part sesquiterpene lactone, the active compound in Arnica, in 10^{1000} parts solution. This dosage is lower than the dosages used in all the studies referenced in the background (Brinkhaus 2006, Seeley 2006, Robertson 2007, Paris 2008, Kotlus 2010) and fewer doses will be delivered than in these previous studies. Patients with new symptoms which may indicate gastroenteritis or internal bleeding will be instructed to return to the Emergency Department for treatment.

In the case of adverse events requiring medical attention, the subject and family will be un-blinded. If the subject is un-blinded prior to completing the study, they will be withdrawn from the study.

Patients who have any of the contraindicated conditions listed in the Risks section will be excluded from the study.

Potential Benefits
Patients receiving Arnica 1M (oral) may experience reduced pain, swelling and/or bruising during the course of their treatment in the study.

The results of this study may provide ED providers with data showing the benefits of a homeopathic treatment for pain, bruising, and swelling to be used in addition to standard of care medication or by itself.

Adverse Events
There are no anticipated adverse events of our study.

Patients experiencing new symptoms due to ingestion of the treatment will be recommended to cease taking the Arnica 1M pills or the placebo. The subject will be withdrawn and un-blinded from the study. The PI will be contacted and may recommend a return to the ED for further work up and treatment. Unanticipated adverse events will be reported to the Institutional Review Board at Children's Hospital as required by the Code of Federal Regulations.

A Data Safety Monitoring Board (DSMB) has been established internally at Children's Minnesota (Appendix 8). The DSMB provides independent safety review and trial guidance during the ongoing trial. The DSMB will periodically meet to review the safety data and results across the treatment groups and will decide if the overall safety and feasibility of the trial remains acceptable. The DSMB will specifically review adverse event data as well as summary reports of all serious adverse events (SAEs) and may review individual cases if deemed appropriate or necessary to determine if a safety concern is emerging. The first meeting will take place after 50 participants have been enrolled or 6 months after recruitment begins and will meet at least annually thereafter.

Stopping Rules and Data Safety Monitoring Plan
The principal investigator and Data and Safety Monitoring Board (DSMB) will monitor data throughout the study and stop or amend the study if there is evidence of a lack of safety and/or efficacy. The members of DSMB are Drs. Stuart Winter, Mike Finch and Kelly Bergmann.

Unblinding Procedures
When the subject develops new symptoms or adverse event that need medical attention, the PI Dr, Madhok will refer to the randomization table to unblind subject.

8. Administrative Procedures

Patient Confidentiality
Data will be recorded in a customized REDCap database residing on the Children's secure network. Access will be limited to the study team. All paper documents associated with the study will be kept in a locked file cabinet accessible only to the study team.

Data Management

Data will be recorded in an electronic database residing on the Children's secure network. Access will be limited to the study team. All paper documents associated with the study will be kept in a locked file cabinet accessible only to the study team. All study documents will be kept for at least three years.

9. References

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10. Appendix

Appendix 1. Parent Take Home Table.
Appendix 2. Instructions for use of homeopathic remedies
Appendix 3. What is Homeopathy?
Appendix 4. Parent Handout
Appendix 5. REDCap form
Appendix 6. Contact Information Sheet
Appendix 7. RA Script
Appendix 8. DSMB