Randomized Controlled Trial of Ultrasound Guidance for Reduction of Pediatric Forearm Fractures
IRB Protocol

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I. PURPOSE OF THE STUDY AND BACKGROUND

Ia. Background and Significance

Ultrasound is now widely accepted as a diagnostic tool for use in the emergency department, as supported by the American College of Emergency Physicians (ACEP) position statement in 2001 (revised in 2008).[1] In addition, the American Academy of Pediatrics (AAP) policy statement in 2015 (also supported by The Society for Academic Emergency Medicine (SAEM), ACEP, and World International Network Focused on Critical Ultrasound (WINFOCUS)) now requires point-of-care ultrasound education for PEM fellowship training[2]. Ultrasound is particularly useful in pediatrics as it is rapid, reliable, portable, easy to use, does not require the patient to remain motionless and does not use ionizing radiation.

Ultrasoundhas been shown to have applications in the evaluation and diagnosis of pediatric skeletal injuries[3,4].There are a number of studies in the literature that support the use of ultrasound in fracture diagnosis. Grechenig et al[5]studied the ability ofultrasound to pick up fractures in cadavers with the goal of delineating the minimum fracture size that could be detected on ultrasound. With the use of high resolution ultrasonography (7.5MHz), cortical discontinuities greater than or equal to 1 mm were identified on all study subjects. Fractures were studied in both longitudinal and cross-sectional views as the authors noted that fractures

[1] American College of Emergency Physicians Policy Statement. Emergency Ultrasound Guidelines. Ann Emerg Med. April 2009;53(4):550-70.
[2]Marin, JR, Lewiss RE, Point-of-care ultrasonography by pediatric emergency medicine physicians. Pediatrics. 2015 April; 135(4):e1113-22
[3]Moritz JD, Berthold LD, Soenksen SF, et al. Ultrasound in diagnosis of fractures in children: unnecessary harassment of useful addition to x-ray? Ultraschall in Med 2008:28:267-274.
[4] Weinberg ER, Tsung JW, Tunik MG. Accuracy of point-of-care ultrasound for the diagnosis of fractures in the pediatric emergency department. Acad Emerg Med. 2008 May; 15(5):S45.
[5] Grechenig et al. Scope and limitations of ultrasonography in the documentation of fractures-an experimental study. Arch Orthop Traum Surg 1998; 117(6-7): 368-71.

could potentially escape detection if the transducer is placed parallel to the course of the fracture. Fractures were demonstrated as either cortical discontinuities or interruptions in acoustic shadows[4,5,6].

Several studies in the pediatric literature have shown that ultrasound can adequately identify long bone fractures, determinethe need for reduction of a displaced fracture and assess the adequacy of reductionwhen compared to plain films.In a prospective study involving pediatric emergency medicine (PEM) physicians by Patel et al[6],ultrasound was compared to plain films to identify fractures, determine need for reduction and assess adequacy of reductionThe study found a 95.5% agreement between ultrasoundand radiography in fracture identification, a 92.3% agreement in need for fracture reduction and a 92.3% agreement in adequacy of reduction.

In a case study, Durston and Swartzentruber[7] described three cases in which ultrasound was helpful in guiding fracture reduction. Chen et al[8], in a prospective study, compared ultrasound to x-ray for the diagnosis of forearm fractures and used ultrasoundas a real-time imaging modality to guide the reduction procedure. They found 97% sensitivity and 100% specificity in the diagnosis of forearm fractures with ultrasound compared to plain films andthe initial success rate of ultrasound-guided reduction was 92% with two patients requiring repeat reduction. Two of 65 fractures were missed, both ulnar styloid fractures in patients who alsohad radial metaphysis fractures and therefore the management was not altered because of the missed diagnosis. However, this study did not compare ultrasound-guided reduction to blinded reduction or reduction with another mode of real-time imaging such as fluoroscopy.

Of note, children tolerate musculoskeletal ultrasound, even in areas of injury, very well. Chien, et al. evaluated the use of ultrasound for the diagnosis of clavicular fractures in children and found that the ultrasound examination was not associated with an increase in pain[9]. While not formally studied, both Patel et al[7] and Chen et al[6] noted that with liberal application of ultrasound transmission gel, there was no worsening of pain andpatients did not require additional pain medication during the ultrasound exam[7].

One pediatric study, by Dubrovsky et al[10],compared the use of ultrasound guided reduction to reduction with fluoroscopy to accurately determine successful fracture realignment. Study physicians used ultrasound to assess the fracture prior to and after reduction, with the option of dynamic visualization during reduction. Fluoroscopic images were obtained after ultrasound images. When comparing the treating physician's interpretation of ultrasound results to a blinded orthopedic surgeon's interpretation of the fluoroscopy results, with a positive test indicating an inadequately reduced fracture, the sensitivity was 50%, specificity 89%, negative

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[6]Patel et al**,** The Utility of bedside ultrasonography in identifying fractures and guiding fracture reduction in children, Pediatric Emergency Care, 2009 April; 25(4): 221-2

[7]Durston, Swartzentruber, Ultrasound guided reduction of pediatric forearm fractures in the ED, Am J Emerg MEd2000 Jan, 18(1): 72-77

[8]Chen et al, Diagnosis and guided reduction of forearm fracture in children using bedside ultrasound, Peds Emerg Care, 2007 Aug; 23(8) 528-531

[9]Chien M et al, Bedside ultrasound in the diagnosis of pediatric clavicle fractures, Pediatr Emerg Care 2011 Nov 27(11); 1038-41

[10]Dubrovsky et al, Accuracy of ultrasonography for determining successful realignment of pediatric forearm fractures, Annals of Emergency Medicine, Ann Emerg Med 2015 Mar; 65(3): 260-5

predictive value was 95.3% and positive predictive value was 28.6%, indicating that ultrasound was best at identifying adequately aligned fractures. Additionally, 78% of physicians indicated that ultrasound was helpful with the reduction procedure.

The use of ultrasound for real-time guidance of fracture reduction compared to blind reduction has been assessed in the adult literature. In a before-and-after study, Ang et al[11], compared ultrasound guided reduction to a retrospective control group who underwent blinded fracture reduction and showed a decreased rate in the number of repeat reductions. In a similar before-and-after study, Chinnock et al[12], showed no significant difference in successful reduction rates with ultrasound compared to blinded reduction.Brahm J et al[13]. in an unpublished abstract, conducted a randomized, single blinded study of adult patients comparing ultrasound guided reduction to standard closed reduction of distal radius fractures and found no difference in the adequacy of reduction, time to reduction or number of repeat reductions between the groups.

It is apparent from these studies that there is a role for ultrasound in guiding fracture reduction. Using ultrasound for dynamic visualization instead of fluoroscopy has several advantages. Ultrasound provides no ionizing radiation, while fluoroscopy exposes the patient, caretaker, and provider to ionizing radiation, requiring shielding forall involved to minimize exposure. Fluoroscopy requires the use of a large, cumbersome machine and many emergency departments, including our institution, are not equipped with fluoroscopic equipment. We intend to build on the studies of Chen et al[9],Patel et al, and others, with a randomized controlled trial to compare the use of real-timeultrasoundguidance of closedforearm fracture reduction to blinded closed forearm fracture reduction in the pediatric emergency department.

Ib. Objectives/Purpose of the study

Our objective is to conduct a prospective randomized trial to assess the utility of using real-time ultrasound imaging in the reduction of forearm fractures in the PED. We also plan to assess provider satisfaction with using ultrasound for the reduction procedure compared to fracture reduction without use of ultrasound. We hypothesize that the use of ultrasound will improve patient outcomes and provider satisfaction. Thus, the primary outcome of the study will be:

1) To compare the number of patients requiring a repeat reduction procedure between the experimental group (ultrasound guided fracture reduction) and control group (standard of care forearm fracture reduction).

Secondary Outcomes:

1) To compare provider satisfaction with the reduction procedure between the two groups. Specifically, we will ask providers to determine:
    I. Providers from experimental group:
        a. Ease of fracture reduction - scale 1-5, (1=easy5=verydifficult)

[11]Ang et al, Ultrasound-guided reduction of distal radius fractures, Am J of Emerg Med, 2010; 28, 1002-1008

[12]Chinnock et al, Ultrasound-guided reduction of distal radius fractures, J of Emerg Med, 2011,40 (3) 308-312

[13] Brahm J et al, A Randomized controlled trial of emergency department ultrasound-guided reduction of distal radius fractures, Annals of Emerg Med-Abstracts, 2011 Oct; 58(4), 230

b. Ease of using ultrasonography on a 5 point scale (1-easy, 5=verydifficult).
c. Was ultrasound helpful in completing the fracture reduction? a) yes b) no c) uncertain

II. Providers from control group:
a. Ease of fracture reduction - scale 1-5, (1=easy5=Most difficult)
b. Do you think real-time imaging would have been helpful for this reduction?

2) To compare the adequacy of reduction between groups by measuring and comparing the degree of angulation and displacement on the post reduction x-rays. An orthopedic surgeon who is blinded to the patient's group assignment will read the x-rays. The acceptable degree of angulation will be the same in both groups. The acceptable degree of angulation based on age is less than 20 degrees' angulation for patients younger than 10 years of age and less than 10 degrees' angulation for patients older than 10 years of age[14].
3) To compare the time for the fracture reduction procedure between the experimental and control group.
4) To compare the number of patients requiring operative repair after reduction between the experimental and control group.
5) To compare the post-reduction ultrasound and x-ray interpretation, including measurement of degree of angulation and displacement on the ultrasound and x-ray for each patient.

Ic. Study Design

The study will be a prospective randomized, controlled, single blinded study. The study is single blinded in that the orthopedic surgeon reading the x-rays and determining the degree of angulation and displacement will be blinded to all patient characteristics and the patient's group assignment.

II. CHARACTERISTICS OF THE RESEARCH POPULATION

IIa. Inclusion Criteria

Patients from 0- 21 years of age, male or female, who present to the Pediatric Emergency Department (PED) with a confirmed displaced forearm fracture that will require reduction by orthopedic surgery in the PEDwill be eligible for inclusion in this study.

IIb. Exclusion criteria

1) Patients with open fractures.
2) Patients with neurovascular compromise.
3) Unstable patients with life-threatening injuries who require ongoing resuscitation.

IIc. Vulnerable subjects:

The population of interest in this study includes patients < 18 years old (i.e. vulnerable subjects). All efforts will be made to protect these children during this study. As mentioned before, ultrasound emits no radiation and is a painless procedure; therefore, this study presents

[14]Daruwalla, JS, 1979; Textbook: Rockwood and Wilkins' Fractures in Children

no risk to these patients. If the patient expresses any discomfort from the ultrasound examination, the procedure will be immediately discontinued and the patient will be removed from the study. The purpose of investigating ultrasound guidance for fracture reduction in this vulnerable population was mentioned in the background section.

IId. Number of Subjects

From a retrospective chart review sampling of displaced forearm fractures requiring reduction from June 1 to August 31, 2015 at CHAM, there were 20 displaced forearm fractures that underwent a closed reduction procedure in the Pediatric Emergency Department. 5 of the 20 displaced forearm fractures (25%) were inadequately reduced and required repeat reduction and/or operative management. Based on a recent study by Wellsh et al, only 6% of patients required repeat fracture reduction when US guidance was used.
In order to observe such a difference with 80% power, the sample size calculation would require a minimum of 56 patients in each group (standard of care vs US-guided reduction) with alpha set at P= 0.05.

Statistical significance will be assessed using mean, percentages, frequency distributions, and p-value. The significance will be set at 0.05. The test statistic used will be the Chi-square test. Confidence intervals will also be obtained.After the primary analysis of the group differences, logistic or normal regression will be used to determine factors related to these outcomes. The significance will be set at 0.05.The statistical approaches will be further developed with the assistance of the statistician in the orthopaedic surgery department following data collection and study approval.

III. METHODS AND PROCEDURES

IIIa. Methods and Procedures

This will be a prospective randomized, controlled, single blinded study that will take place at the Children's Hospital at Montefiore (CHAM) in the Pediatric Emergency Department (PED). Patients who present to the PED, are confirmed to havea forearm fracture requiring closed reduction in the PED and meet the inclusion/exclusion criteria will be eligible for the study. The decision to perform a closed reduction procedure in the PED will be made by the consulting orthopedic surgeon who will perform the procedure. All eligible patients' pain will be reassessed and managed as necessary as per standard of careThe eligible patient or parent/guardian will be approached by the treating physician or consulting orthopedic resident for written consent. Written assent will be obtained from minors older than 7 years of age (see below for consent timeline/process).After enrollment into the study, patients will be randomized to either the experimental group (ultrasound guided fracture reduction) or control group (standard of care forearm fracture reduction without real-time imaging). Allocation of patients to intervention and control arms will be accomplished by a computer-generated permuted block randomization scheme.An individual in the Department of Orthopaedic Surgery,who is not part of the study team will perform block randomization and will provide the study team with sealed envelopes for treatment prior to the enrollment of any patients in the study. These envelopes will be part of the study package, which include study questionnaires.We will choose blocks of 20 patients in order to reduce or eliminate experimental error contributed by inexperience using the US-guidance at the beginning of the study.

Consulting orthopedic residents will be trained to perform musculoskeletal sonography for this study (see below for standardized training of study physicians in ultrasound) and will be considered study-trained physicians. All patients will undergo procedural sedation and/or pain management for closed reduction as per standard of care in the PED. The medication used for sedation and/or pain will be determined by the treating PEM physician. Study patients that are randomized to the ultrasound guided group will undergo a point-of-care ultrasound, performed by a study trained physician using a Sonosite Edge ultrasound machine with an L38 linear 10-5 MHz transducer probe.

Prior to the reduction procedure in patients randomized to the experimental group, ultrasound images of the fracture site will be obtained and the maximum degree of displacement will be measured. The ultrasound technique involves placing ultrasound gel over the fracture site and then placing the ultrasound probe in contact with the gel but not with the underlying skin. Both longitudinal and transverse views of the injured area will be obtained. Fractures are identified as an irregularity or interruption of the cortex of the bone.The degree of displacement is measured by drawing two intersecting lines along the edge of the cortex at the fracture site, generating an angle. Displacement measurements are then made by calculating the distance from the normal cortex to the fractured edge of the cortex.

The trained physician will then perform real-time ultrasound imaging as neededduring the closed reduction procedure. Real-time ultrasound imaging includes both longitudinal and transverse views of the fracture site, repeated as often as necessary until the best alignment can be obtained. Once the orthopedic resident determines that he/she has obtained optimal alignment and prior to casting, a post-reduction ultrasound image will be obtained and the angle of displacement will again be measured. All ultrasounds performed prior to and after the reduction will be recorded, and the images obtained will include video clips of the ultrasound as well as a saved still picture of the best image of the suspected fracture site.The study-trained physician who performed the ultrasound will then record his/her findings on the data collection form immediately after the procedure and prior to reviewing plain radiographs.

While it has been our experience that the majority of reduction procedures performed in the PED are done without the use of any real time imaging, some orthopedic surgery residents employ the use of the c-arm (fluoroscopy) and/or a portable x-ray machine during the reduction procedure. At his/her discretion, the orthopedic resident may use either of these modalities in both the ultrasound and control group as per standard of care in the PED. The use of these modalities will be recorded.

After the reduction procedure in the ultrasound group and prior to reviewing the post reduction x-ray, the orthopedic residentwill complete a brief questionnaire with the following questions.

For the experimental group:

a. Rate the ease of fracture reduction from 1-5, (1=easy 5=Verydifficult)
b. Was ultrasound helpful in completing the fracture reduction? a) yes b) no c) uncertain
c. Rate the ease of using ultrasonography on a 5 point scale (1- easy, 5=verydifficult).

The control group will undergo fracture reduction without ultrasound guidance as per the current standard of care in the PED. After the reduction procedure in the control group, the orthopedic resident will complete a brief questionnaire with the following questions:

For the control group:

a. Rate the ease of fracture reduction from 1-5, (1=easy 5=very difficult)
b. Do you think real-time imaging would have been helpful for this reduction?

After the reduction andcasting is completed, patients in both groups will undergo a post-reduction x-ray. Based on the degree of displacement on the x-ray, the orthopedic surgeon will determine whether the patient needs a repeat reduction, as per routine standard of care.If a repeat reduction is required, the treating physician can choose to use ultrasound at his/her disgression.The angle of displacement will be measured on the post-reduction x-ray by an orthopedic surgeon. Additionally, the angle of displacement measured on the post-reduction ultrasound will be measured and compared to the angle of displacement on the post-reduction x-ray. An expert sonographer will review cases where the ultrasound and x-ray results do not correlate.

IIIb. Data Collection / Monitoring

The primary endpoint of the study is comparing the percentage of patients with an adequate degree of angulation on post-reduction x-rays between the experimental group and the control group. X-rays will be performed based on the PED routine standard of care. Demographic data recorded by the study trained physician will include the patient's name, age, medical record number, date of birth, date of visit, and ultrasound experience of the study-trained physician performing the ultrasound. *The patient identifiers are necessary for patient tracking to match ultrasound findings with X-ray final readingsand for clinical follow up*.Type of sedation used, length of procedure and any ultrasound data will be collected and recorded by study trained physicians. Radiographic readings will be collected by the investigators.

IIIc. Data Storage and Privacy

The principal- and co-investigators will manage the data generated and oversee quality control measures for the study in order to ensure the confidentiality of data at all times, as mandated under HIPAA.

All data collected during the study will be treated as confidential information by all involved staff. Patient identifier information will be located on only one form that will be destroyed upon completion of the study, after data is cleaned, analyzed and published. Patients will be assigned a study number to protect confidentiality, which will be used on all other data sheets to ensure that patient identifier information is located on only one protected form.

Data forms will be kept in a secure locked file in a locked office. The data sheet containing patient identifier information that will allow follow-up and act as a key to the unique study identifier number will be separated from the clinical data forms and stored in a separate locked cabinet. HIPAA-sensitive Personal Health Information (PHI) will not be reused or disclosed to any other person or entity, except as required by regulation and law or for authorized oversight of the research project.

All patient data stored on the ultrasound machine will be saved under their study patient number without patient identifiers.

IIId. Study Equipment

The study intervention will be the use of bedside ultrasound to guide reduction of forearm fracture reduction. A Sonosite Edge ultrasound machine with an L38 linear transducer probe 10-5 MHz will be used for point-of-care ultrasound.

IIIe. Standardized Training of Physicians in Ultrasound

Prior to beginning this study, all participating consultingorthopedic residents and PEM attendings and fellowswill participate in a one-hour training session which will teach the basics of how to use ultrasound to diagnose fractures. PEM physicians and ortho residents have a foundation in emergency ultrasound, and the training session will build upon this background knowledge and teach the specific skills necessary for musculoskeletal ultrasonography of the forearm. In addition, this session will standardize the method in which bedside ultrasound will be performed by participating physicians. The training session at CHAM will be taught by study investigators.The session will begin with a formal PowerPoint presentation, complete with ultrasound images and videos of fractures, which will be followed by a practical session where participants will perform ultrasound of intact and simulated fractured bones to visualize both normal and fractured cortex. There will be a post-training assessment conducted by study investigatorsto ensure that all co-investigators are adequately trained to enroll patients. In previous studies, ED physicians with minimal training were able to successfully perform ultrasound studies throughout the course of each study[7,11,12]. We will also provide a teaching manual for reference complete with images and instructions.

IV. RISK/BENEFIT ASSESSMENT

IVa. Potential Risks and Benefits

There are no known risks to ultrasound, with no reports of adverse events in over 50 years of clinical use. The use of ultrasound is painless by avoiding contact of the ultrasound probe with the injured body part and solely maintaining contact with the ultrasound gel. The ability of patients to tolerate ultrasound of injured areas, without pain, is well documented in the literature.Patel et al[6] reported that "it was our observation that the bedside ultrasound examination did not exacerbate pain."In a study of ultrasound-assisted diagnosis of pediatric ankle fractures, Simanovsky reported similar findings: "All the patients were cooperative and tolerated the procedure well".[15]

During the process of data collection, patient identifiers will be collected (name, age, medical record number, birth date, date of visit). As mentioned previously, this identifying information is necessary for x-ray follow-up and will be located on only one form. This form with identifying information will be kept in a locked file cabinet in a locked office. All other data sheets and saved data will be organized by an assigned patient number.

IVb. Protection against risk

In the unlikely event that a patient is unable to tolerate the ultrasound procedure, the ultrasound will be discontinued immediately and the patient will be removed from the study. There are no infectious risks from the use of ultrasound in this study; open fractures are excluded, and the US machine will be cleaned per routine procedure after each use.

The risk of patient confidentiality being violated in this study is minimal due to the numerous safeguards that have been implemented (see section IVa).

[15] Simanovsky et al. Sonographic detection of radiographically occult fractures in paediatric ankle injuries. Pediatr Radiol 2005; 35(11):1062-5.

V. INVESTIGATOR QUALIFICATIONS AND EXPERIENCE – see attached CV

VI.SUBJECT IDENTIFICATION, RECRUITMENT AND CONSENT/ASSENT

VIa. Consent and Procedure Timeline / Process

The PEM attending, fellow or orthopedic resident caring for the patient will determine if the patient is eligible for inclusion in this study. If the patient is eligible and does not meet any of the exclusion criteria, the patient will be asked to participate (see written consent and child assent documents). The patient will be randomized to one arm of the study only after obtaining written consent from the patient ≥ 18 years of age or the parent/guardian of a minor and assent if the child is ≥ 7 years.

The experimental group will have an ultrasound performed prior to, duringand after forearm fracture reduction. The ultrasound procedure involves placing ultrasound gel over the fracture site. The ultrasound probe is then placed in contact with the gel but not with the underlying skin. Images of the bony cortex are obtained in both longitudinal and transverse orientations and recorded on the ultrasound hard drive. After completion of the post-reduction ultrasound, the ultrasound gel will be removed, and the patient will undergo routine casting/splinting andpost-reduction x-ray as per thePediatric ED standard of care. The control groupwill undergo the standard of care fracture reduction with post-procedure x-ray images.

While it is possible that the procedure with ultrasound will take longer than standard of care closed reduction, it is also possible that the procedure time will be the same or shorter. In the abstract by Brahm et al[13], they found no difference in time for fracture reduction between the two groups. Based on prior studies, we do not anticipate that patients participating in this study will incur significant delays in routine care based on their participation.

The alternative treatment for patients/parents who do not want to participate in this study will be fracture reduction without ultrasound.

VIb. Subject Identification/Recruitment/Consent

Potential subjects will be recruited by PEM attendings, PEM fellows and orthopedic residents who have participated in the formal ultrasound fracture diagnosis training session. Subjects will be recruited solely on the basis of inclusion and exclusion criteria. The consent/assent will be obtained and then documented by the study trained physician who is performing the ultrasound.

VIc. Subject Capacity

The only subjects in this minimal risk study that may meet criteria for limited capacity would be children. We have put several safeguards in place to provide full protection to this group: consent provided by a parent/guardian, assent provided by a child over seven years, and an assent script in which the study is described in basic language appropriate to a seven year old child.

VId. Subject Comprehension

We will provide consent documents to guarantee a standardized delivery of information when obtaining consent. By using basic language that is easy to understand for a seven year old child, we will maximize the patients' comprehension of the study.

VIe. Consent Forms / Documentation of Consent

Please see attached consent and assent forms. We will seek IRB approval of a translated consent/assent form in Spanish after IRB approval of the English consent/assent forms.

VIf. Costs and Compensation to Subjects

There will be no costs or compensation to subjects taking part in this study.

VIg. Potential Conflict of Interest and Funding

There will be no funding for this study. No funds will accrue to any of the investigators. No funding is sought or exists from commercial sources, and no relationship exists or is sought with any commercial company.

VII. Data Safety Monitoring

The PI and study coordinator will monitor data and safety, with emphasis on data integrity and patient safety concerns including: review of adverse events, recommendations concerning continuation or conclusion of the study, protection of the confidentiality of the trial data and the results of monitoring, review of data and study quality. Any adverse events, unanticipated problems, and protocol deviations will be reported to the IRB.