Title: The Diagnostic Accuracy of Pocket Size Ultrasound (PsUS) in the Detection of Pediatric Elbow Fractures

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Background:

According to the World Health Organization (WHO), between 66-75% of the world's population has no or limited access to diagnostic imaging (WHO, 2003, WHO, 2010 & Morris et al). Given this critical need for imaging, especially in regards to devices that are reliable, portable, and easy to use, ultrasonography has emerged as a valuable, non-invasive imaging option and increasingly being used in resource limited or restricted areas. Beyond its growing use in global health, bedside point-of-care ultrasound (POCUS) is also a rapidly evolving imaging modality with multiple well-established and novel applications. One example of a promising direction for POCUS is in the evaluation of pediatric upper extremity fractures.

Pediatric fractures are common injuries in childhood, with between 25% and 50% of children sustaining a fracture before the age of 16 years old (Rennie et al, Merckaert et al). Musculoskeletal injuries often present to the pediatric emergency department (ED) and contribute to at least 30% of ED visits in school-aged children, of which 28% are fractures (Alpern et al, Poonai et al, Lee A et al). The most frequent location of pediatric fractures is in the upper extremities, with the most common locations being the distal forearm, fingers, and distal humerus (Rennie et al, Naranje et al, Lee A et al, Merckaert et al). Focusing specifically on elbow injuries, about 5-10% of pediatrics fractures are located in the elbow, with 60-80% of injuries involving the supracondylar humerus (SCH) (Crowther et al, Bellavia et al, Merckaert et al). Prompt diagnosis is critical in cases of SCH fractures as the potential for malunion or neurovascular injury are serious complications that occur at a high rate in children (Crowther et al, Bellavia et al,).

The standard diagnostic imaging of choice for elbow fractures is radiography with multiple views, typically anterior/posterior and lateral views (Ackermann et al 2010). However, radiographs are associated with exposure to ionizing radiation and, although in only small amounts, the effects of radiation are considered cumulative with repeated imaging increasing a patient's health risks over their lifetime (Charr-Alvarez 2011). Additionally, in children with a clinical suspicion for a fracture, an estimated 83% of X-ray scans performed show no fracture (Ackermann, 2020]. Besides the majority of X-rays which do not show signs of fracture, initial radiographs can also miss occult supracondylar fractures in 2-18% of all fractures seen in subsequent follow-up imaging (Burnier et al 2016). Ultrasound offers an alternative imaging option that avoids ionizing radiation and an opportunity to reduce a child's lifetime radiation exposure. In addition to the avoidance of radiation, ultrasound also has the benefits of being portable to the bedside, rapid to perform, and noninvasive, which all makes it especially well suited for use with children (Barata 2012, Charr-Alvarez 2011, Chen 2007). According to one study, ultrasound can also cut down on the time to diagnosis and even pain when compared to radiography (Charr-Alvarez 2011).

Ultrasonography is able to visualize normal bone cortex as bright hyperechoic lines with shadowing posteriorly on ultrasound, and fractures appear as cortical disruptions or discontinuities bone contour (Barata 2012, Eckert 2013). As for cartilaginous portions of bone, the epiphysis appearance ranges from anechoic to hypoechoic with a hyperechoic epiphyseal core depending on the patient's age and stage of bone maturation (Eckert 2013). Fractures can also appear as indirect signs including posterior fat pad, lipohemarthrosis, subperiosteal hemorrhage, articular effusion, and

accompanying peri-osseous soft-tissue injuries (Ackermann, 2020, Cho 2010, Burnier et al). Specifically for visual signs of elbow fractures, both direct signs (e.g. cortical disruptions or discontinuities in the bones' contour) as well as indirect signs (e.g. posterior fat pad with or without lipohemarthrosis) can indicate a potential fracture injury to the elbow.

In terms of the accuracy and reliability of bedside POCUS, several decades of research has examined the use of ultrasound in the assessment of pediatric upper extremity fractures, with encouraging results with high-end, hospital-grade ultrasound machines. According to a meta-analysis from 2019, Lee et al showed summary sensitivity and specificity of 96% (95% CI 88-99%) and 89% (95% CI 82-94%), respectively. These findings were comparable to the findings of a recent systematic review and meta-analysis by Tsou et al in 2020 where the overall sensitivity and specificity of ultrasound for pediatric upper extremity fractures was found to be 0.95 (95% CI: 0.93–0.97) and 0.95 (95% CI: 0.91–0.98), with a positive likelihood ratio of 21.1 (95% CI: 10.8–41.5) and negative likelihood ratio of 0.05 (95% CI: 0.03–0.07). However, in a specific meta-regression for analysis of elbow vs non-elbow upper extremity ultrasound, there was a significantly lower specificity for elbow fracture when compared to other upper extremity fractures. This finding may be explained due to the complex anatomy of the elbow joint which makes these scans technically more challenging to perform and interpret.

As technology has advanced in the field of ultrasonography, there have been exciting developments in pocket-sized ultrasound (PsUS) units. These smaller hand-held devices have been found to have overall good agreement with high-end ultrasound machines, with specific limitations to distinct clinical questions, according to a recent systematic review comparing handheld to high-end ultrasound systems (Rykkje et al, 2019). However these units are often a fraction of the cost of the larger hospital grade machines and less cumbersome to travel with (Lau 2017). As a result of their smaller, more convenient size and affordable price, these pocket-sized ultrasound devices pose a particularly interesting question in regards to their application in more remote or resource-limited settings. The current research of PsUS is limited with only a handful studies evaluating fractures, typically in older adolescents and adults. Lau et al in 2017 investigated the validity and reliability of PsUS in the diagnosis of distal radius fractures in adults and assessment of closed reductions, finding a sensitivity of 100% and specificity that ranged from 90% to 95% (Lau et al). These results supported the idea that PsUS may serve as a useful screening tool for the diagnosis of distal radius fracture, similar to the findings for larger hospital grade units. Another study by McNeil et al. found similar findings in the accuracy of portable US in diagnosing fractures in austere environments with an impressive overall sensitivity of 100% and a specificity of 94%.

Despite this growing area of research, limited data exists for the evaluation of pediatric fractures with portable ultrasound and, to our knowledge, no study has been performed investigating the accuracy of a PsUS on the assessment of pediatric elbow injuries. The long-term goal of this research is to investigate the use of a PsUS device in the assessment of pediatric upper extremity fractures in resource-limited or -restricted areas. To achieve this goal, we must advance our understanding of pocket-sized ultrasonography and determine the validity as well as the reliability of these smaller devices in fracture assessments. We propose a study that investigates the use of PsUS in the evaluation of pediatric elbow injuries with comparison to the physical exam and standard radiography. The main purpose of this prospective study is to determine diagnostic accuracy of PsUS in detecting signs of acute elbow fractures. If accurate and reliable, these handheld ultrasound

devices could be an impactful and noninvasive method for delivering imaging to resource limited areas, improving the diagnostic capabilities of remote regions of the world.

Objectives

Aims

1. Evaluate the sensitivity (SE), specificity (SP), positive predictive value (PPV), and negative predictive value (NPV) of pocket-sized ultrasonography for the assessment of acute pediatric elbow fractures.
2. Evaluate the inter-rater reliability between examiners and blinded ultrasound expert.

Hypothesis

3. We hypothesize that PsUS will have similar SE, SP, PPV, and NPV to gold standard radiographs for pediatric elbow fracture evaluation.
4. We hypothesize that interpretation of PsUS imaging will be similar between bedside interpretation and blinded expert ultrasound interpretation.

Methodology

Study Design

This will be a two part study involving first a brief feasibility portion followed by a prospective non-inferiority study conducted from winter 2021 to winter 2022 in an urban pediatric level 1 trauma center and emergency department (Comer Children's Hospital in Chicago, IL). The duration of the study will continue through to 2023 for biostatistical analysis and data publication. This study will be reviewed and approved by the University of Chicago Institutional Review Board.

Part 1: Feasibility Study

In order to establish that pocket-sound US users are able to obtain accurate and adequate imaging for interpretation, the study will first start with a brief 1 month feasibility study. This portion of the study will involve each of the study providers and will consist of the initial training, consent of feasibility participants, and image obtainment.

Study Training:

Before the start of the study, all participating pediatric emergency medicine attending physicians and fellows will be trained on how to use a PsUS and how to perform the elbow exam for

a suspected elbow fractures. Training will consist of both didactic and hands-on components over a brief training session along with pre/post survey for bedside sonographers. Standardized views will include both longitudinal and transverse views of the posterior and anterior elbow, longitudinal lateral and medial views of elbow, and finally views of the proximal ends of both radius and ulna for signs of fracture. This specific group of sonographers is selected to perform the ultrasound exam as they will all have at least a basic knowledge of how to perform ultrasound as well as past general scanning experience of at least 1-2 years. Beyond this initial training, an education reference tool with images and instructions will also be present in the ED for reference for study providers during the duration of the study.

Feasibility Protocol

Once trained, each study provider will obtain 3 elbow exams of participants between the ages of 1-16 years old over 1 month. Each provider will use the standardized views reviewed in the ultrasound training to perform the exam. Verbal consent will be obtained from each participant's parent for inclusion in the feasibility study. Images will be stored on the password protect, user-specific, cloud storage butterfly image database and then reviewed by study staff for accuracy as well as for quality of standardized US views. No identifiable information about participants will be saved including no name, initials, DOB, or MRN. The study providers performing the exam will initial their studies in order to keep track each provider has performed 3 elbow exams. These images will only be reviewed by study staff to ensure US examiners are correctly obtaining the standardized views needed for a formal interpretation but will not be reviewed by an expert for interpretation as these images will be used only for feasibility, not hypothesis testing.

Part 2: Non-inferiority Study

Once the feasibility study is complete, the study team will began the recruitment and protocol for non-inferiority study. See Appendix 1 for part 2 non-inferiority study schematic.

Recruitment & Selection of Participants:

A convenience sample of pediatric patients with isolated acute elbow pain will be recruited for this study. Patients will be identified after initial emergency room triage when an acute isolated elbow injury is identified as a primary ED complaint. Participants and parents/guardians will initially be approached by study-affiliated providers in order to introduce study and determine potential interest. Study-affiliated providers will include study trained pediatric emergency medicine (PEM) attending physicians and fellows. As there is often only one attending physician or fellow in the Comer ED, this may involve the treating physician for the patient. If interested, participants will be enrolled when a PEM attending physician or fellow is available to consent patient and/or parent/guardian, prior to the completion of additional study steps (i.e. completion of PsUS elbow exam). Following signing of consent, PsUS exam will be performed by study-affiliated and -trained PEM attending or fellow. Study recruitment information will be posted in primary ED clinical staff area to spread department awareness of this study and facilitate communication to study providers of a potential participant in the ED. In addition, electronic study announcements will also be sent to department staff to introduce and spread awareness of the study. Eligibility criteria will be reviewed by study providers prior to introduction or enrollment of any subjects into the study. Recruitment will be complete once 70 participants have been recruited and consented into the study.

Inclusion criteria will include children between the ages of 1-16 years olds, with isolated, acute (less than 48 hrs) elbow pain in the setting of adequate history of trauma. Suspected elbow fractures will be defined as pain, tenderness, swelling, and/or the inability or unwillingness to move the elbow joint in the full range of motion.

Exclusion criteria will include patients <1 or >16 years old, those with open fractures, gross deformities, multiple traumatic injuries, distal neurovascular compromise, unstable vital signs or hemodynamic instability, altered mental status, history of skeletal abnormalities, or past elbow fracture as well as wards of the state or those unable to provide consent. Patients who receive radiography or a confirmed diagnosis of fracture at an outside institutions prior to arrival to the ED will also be excluded.

Consent Process

Once a potential research participant is identified by emergency staff, study will be introduced to subjects and parent or guardian. If patient and/or parent/guardian is interested in study, informed consent will be obtained by either pediatric emergency medicine attending physicians or fellows in accordance to IRB consenting process at University of Chicago. Study procedures, risks, and benefits will be explained in detail to patient and parents/guardians. As all patient's will not be of age to consent independently, written informed consent will be obtained from patient's parents or guardians, with informed assent obtained when applicable for age per assent guidelines by the University of Chicago IRB assent guidelines. Subjects will either sign the assent form (7-12 yo when medically able to sign) or the assent line of the consent form (12-16 yo who have the cognitive capacity to understand the consent form). Study protocol and purpose will be explained in terminology appropriate for age. Consent will be obtained in the emergency room after initial triage of acute, isolated elbow pain but before ultrasound of the extremity. The consent and assent process will take place at the subject's bedside. Once consented, an ultrasound-trained study staff member will perform the bedside PsUS exam.

Risks and Benefits:

This prospective study does not involve any medications, experimental drugs or invasive procedures. The pocket-sized ultrasound (PsUS) exam is a non-invasive device that uses high frequency sound waves to visualize underlying structures with no associated radiation. The associated risks of bedside PsUS ultrasound exam are minimal and the exam will be limited to 5-10 minutes. The gel used during the ultrasound exam may be cold and the probe may apply light pressure on the elbow during the exam. There may be mild pain during the application of this pressure which can be minimized with ample gel application. Otherwise there are no additional physical or psychological risks or side effects associated with the PsUS exam and no financial, social or legal risks have been identified with the study. Subjects will continue to received gold standard of care for elbow injury evaluation and any disruption to care with be minimized due to rapid nature of the exam and preexisting waiting period in emergency room.

There is also minimal risk to loss of confidentially as information will be coded and de-identified whenever possible. Ultrasound image data will be de-identified and stored on secure password-protected, encrypted, HIPAA-compliant web-based database (for more information on encryption and security of Butterfly ultrasound imaging database see: https://assets.website-files.com/5a0cbe08f1138d000147a9d4/5f87cf6e54026165cc910baf_Butterfly%2BNetwork%2BTechnology%2Band%2BSecurity%2BWhite%2BPaper%2B950-20009-00%2Brev%2BE.pdf). Any

additional personal health information will be stored on University of Chicago RedCAP database. Each subject will be given unique study number with no personal health information that will be used in both the web-based ultrasound image database and in RedCAP. The unique study identifier will be written on the study's copy of the consent form in order provide study investigators a method to link ultrasound imaging back to the medical chart. When data is reviewed for blinded US expert review or for biostatistical analysis, raw data will be fully de-identified with no personal health information. All consents will be stored in a locked cabinet in a locked office.

There are no direct benefits to the patients participating in this study. The patients will not be informed of the results of the ultrasound exam as these results will be used for research only. As standard of care of elbow injury (i.e. radiographs) will still be determined and completed as clinically indicated, ultrasound results will not contribute to clinical decision making by primary ED team. Potential future benefits of this study include validating the use of bedside PsUS to evaluate acute elbow fractures in a pediatric population. This benefit is especially promising in areas without or limited access to more advanced imaging.

Study investigators plan to review images monthly to ensure standardized sonography views of elbow are being captured. Additionally study investigators also plan to communicate with study sonographers every month to check in regarding study logistics, challenges, or issues that might be encountered during completion of the study. This will also be an opportunity to review any safety concerns or adverse events. Any adverse events or unanticipated problems will be reported immediately to University of Chicago IRB through the online Aura IRB portal. No data safety monitoring board (DSMB) will be utilized for this study and this study does not have sponsor or FDA involvement.

Cost, Compensation and Incentives

The subjects will not incur any additional costs as a result of their participation in this study. There will be no compensation or incentives offered to subjects for their involvement in this research study.

Study Protocol

Once consented, a PsUS elbow exam will be performed on every participating subject using a single handheld 2D array universal probe of the Butterfly IQ pocket sized ultrasound machine (Butterfly Network, Guilford, CT, USA), connected to the study ultrasound examiner's smart phone. The device will use factory standard settings and all images will be acquired using room temperature Aquasonic 100 Ultrasound Transmission Gel (Parker Laboratories, Fairfield, NJ, USA). The exam will take approximately 5-10 minutes to complete.

Bedside ultrasound examiners will perform the elbow PsUS exam as follows:

1) Place the injured elbow in the most comfortable position for the patient, as ultrasound exam can be performed in almost any position. Apply copious ultrasound gel to probe prior to placement onto elbow to reduce pressure applied to injury, minimizing potential pain or discomfort with exam.
2) Start exam in dorsal aspect of the distal humerus, obtaining both longitudinal and transverse views of the posterior elbow.
3) Next, move probe to ventral aspect of distal humerus and obtain both longitudinal and transverse views of the anterior elbow

4) Then, move probe to sides of elbow to obtain longitudinal lateral and medial views of elbow
5) Finally include views of the proximal ends of both radius and ulna for signs of fracture.

The contralateral uninjured elbow will be imaged for comparison immediately following injured elbow. This will result in a set of standardized views of the elbow being obtained from each patient, with both still and video clips of each orientation being recorded. A positive PsUS will be defined as the presence of signs of elbow fracture, either as direct signs including cortical disruptions or discontinuities in the bones' contour or indirect signs including posterior fat pad with or without lipohemarthrosis on ultrasound exam.

After performing the ultrasound, all relevant ultrasonographic images will be stored on a password protected, cloud-based imaging database provide by the Butterfly Network, with all identifying information removed. Immediately after the exam, a basic assessment of the ultrasound images will be asked of each of the bedside ultrasound providers, as positive, negative or equivocal for signs of elbow fracture, but before reviewing any radiographic imaging studies. In addition, the stored images will also later be reviewed and interpreted by a blinded physician who has extensive ultrasound experience and limited clinical knowledge beyond patient's age, sex, and complaint of elbow pain (blinded to additional clinical knowledge, bedside interpretation and radiographic findings). Both the bedside and expert ultrasound interpretation will also be compared to the final fracture diagnosis. Additionally, quality assurance of imaging by bedside examiners will be reviewed during the first four months of the study to ensure appropriate acquisition of standardized views by different ultrasound exams by the study investigator.

Following the ultrasound exam, patients will undergo standard clinical care for acute elbow injury per primary ED team, which could consist of anterior/posterior and lateral radiographs of the elbow in accordance to the standard of care for suspected elbow fractures or bedside reduction in cases of suspected radial head subluxations. Results of the ultrasound exam will be blinded to the radiology team with the final readings of the x-ray images by the blinded radiology team obtained from patient's chart by study investigators after the patient encounter. Preceding pain management and subsequent clinical management of patient will be based on the primary ED teams' clinical assessment and radiographic findings. In addition to review of initial radiographic findings, in cases of negative fracture, subsequent follow up imaging when applicable will also be checked and reviewed for the presence of any occult fractures. Subsequent radiographic imaging will be at the discretion of the primary ED team or orthopedic consultants. A positive diagnosis of an elbow fracture will be defined as radiographic evidence of acute fracture (or healing fracture if during follow up imaging) or cortical irregularity on imaging by final clinical report by the pediatric radiology attending on service. In cases where no follow up imaging is obtained, the clinical diagnosis of no fracture will be confirmed by assumed resolution of clinical symptoms. Additionally, research staff will also attempt to make 1 follow-up phone call to participants 1 month after their ED visit for their elbow injury to determine if any additional radiographic imaging or care was obtained and if subsequent occult fractures were discovered on later imaging that may have been missed on the initial evaluation. No additional direct patient interaction will occur with subjects after this follow up phone call.

Data collection for all study subjects will include basic demographic characteristics (Age, Sex, MRN), initial physical exam findings, radiographic elbow images, and final radiography reports

of images. All study data will be stored in secure, HIPAA-complaint data collecting system called RedCAP. De-identified ultrasound image and redcap data will be stored for 5 years on secure servers after the study manuscript is published. After this period, all study documents linking subject PHI to the coded dataset will be deleted or destroyed and a de-identified dataset including ultrasound images will be retained for educational purposes indefinitely.

Outcome Measures & Primary Data Analysis

We will evaluate the diagnostic accuracy of the PsUS findings by comparing it to reference standard of radiography when indicated for suspected elbow fractures. Both ultrasound and radiography will be performed and interpreted independently to the each other, with imaging results blinded to ultrasound examiner/radiologist at the time of imaging review. We will also compare the findings of both of the expert interpretation and the bedside assessment of the PsUS exam to the radiographic findings. We will calculate sensitivity (Sn), specificity (Sp), positive predictive value (PPV), and negative predictive value (NPV). In addition, inter-rater reliability with Cohen's kappa statistic will also be calculated to compare the agreement between the two ultrasound examiners. Data will be analyzed using statistical analysis for a non-inferiority study model, with a significance level defined as $p<0.05$, with goal power of 0.8 (80%), and confidence interval of 95%. We will be using a one-sided equivalence test of correlated proportions with the estimated maximum allowable difference between these proportions that still results in equivalence (the range of equivalence) being 0.06. The estimated sample size from these calculations is 70 children for this non-inferiority study.

Timeline

Submit to IRB	July 2021
Estimate approval	Winter 2021
Begin Study	Winter 2021 (pending approval)
Enrollment though	December 2022
Review Data	Winter 2022
Publish/Present Results	Spring 2023 (Goal: 2021 PAS (Spr) vs AAP 2023 (fall, post fellowship))

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Appendix 1: Study Schematic