Randomized Clinical Trial Evaluating Acutrak Headless Compression Screw Fixation of Medial Malleolus Fractures

Study Protocol and Statistical Analysis Plan

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Randomized Clinical Trail Evaluating Acutrak Headless Compression Screw Fixation of Medial Malleolus Fractures

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INTRODUCTION

Medial malleolus fractures can arise from the application of axial force at various anatomical positions of the ankle. Supination-external rotation, pronation-external rotation, or pronation-abduction results in an oblique fracture pattern. Supination-adduction results in a vertical shear fracture pattern. Multiple techniques have been described for fixation of the medial malleolus.[1,2] The AO group currently advocates two parallel 4.0 mm partially threaded cancellous screws oriented perpendicular to the fracture line to provide compression as the gold standard for medial malleolus fixation.

Static load to failure testing our laboratory has challenged this observation in horizontal medial malleolus fracture patterns.[3,4] We previously demonstrated superior stiffness (178 ± 26 N/mm) and load at 2 mm of ankle joint displacement (362 ± 72 N) with a contoured mini-fragment T-plate fixation versus two parallel 4.0 mm cancellous screw fixation (141 ± 24 N/mm and 292 ± 47 N, respectively) and tension band wire fixation (124 ± 16 N/mm and 267 ± 43 N, respectively) of horizontal medial malleolus fractures ($p < 0.05$).[3] We recently demonstrated (manuscript submitted) contoured mini-fragment T-plate fixation is biomechanically equivalent to bicortical screw fixation with respect to construct stiffness (684 ± 101 N/mm and 668 ± 61 N/mm, respectively) and load at 2 mm of ankle joint displacement (239 ± 83 N and 240 ± 17 N, respectively) in static load to failure testing of horizontal medial malleolus fractures. However, both constructs were superior to unicortical screw fixation (392 ± 34 N/mm and 102 ± 20 N, respectively) of horizontal medial malleolus fractures ($p < 0.05$).

Static load to failure testing our laboratory has challenged this observation in vertical medial malleolus fracture patterns as well.[5-7] We recently demonstrated (manuscript submitted) superior stiffness (463 ± 91 N/mm) and load at 2 mm of ankle joint displacement (922 ± 297 N) with antiglide plate fixation versus unicortical screw fixation (111 ± 35 N/mm and 284 ± 51 N, respectively) and bicortical screw fixation (279 ± 30 N/mm and 429 ± 112 N, respectively) of vertical medial malleolus fractures ($p < 0.05$).

Superior fixation requires extensive dissection and fixation known to result in prominent hardware and hardware related pain. None of these fixation methods address the lack of soft tissue to cover the medial malleolus and the common practice of hardware removal to address post-fixation hardware pain. Retrospective review of ankle hardware removal cases indicates that 6% (8/126) of patients have their hardware removed for non-pain issues (e.g., infection, etc.) at 6 months and 17% (22/126) of patients have their hardware removed for pain on the medial or lateral side of the ankle at 6 months.[8]

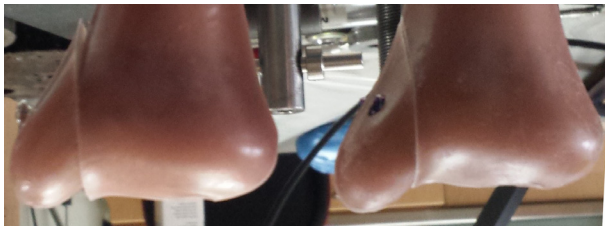

Figure 1: Vertical shear medial malleolus fractures fixed with cancellous screws (left) and Acutrak screws (right) demonstrating the lack of hardware prominence after fixation as well as maintenance of reduction after off-set axial loading.

The headless configuration of the Acutrak system makes it ideal for medial malleolus fixation and may obviate the need for hardware removal. We recently demonstrated (manuscript submitted) superior stiffness and load at 2 mm of ankle joint displacement of an Acutrak screw construct (244 ± 58 N/mm and 483 ± 91 N, respectively) when compared to partially threaded parallel unicortical cancellous screw construct (111 ± 35 N/mm and 278 ± 49 N, respectively) in static load

to failure testing of vertical medial malleolus fractures. Additionally, when the specimens were displaced to 6 mm and allowed to relax, the Acutrak headless compression screw constructs reduced to the pretesting fragment alignment while the parallel cancellous constructs remained displaced (see Figure 1).

HYPOTHESIS

The fixation provided by the Acutrak headless compression screws provide sufficient fixation to achieve union and a favorable clinical outcome in both horizontal **and** vertical medial malleolus fractures when compared to bicortical and unicortical screw fixation, tension band wiring, and mini-fragment or buttress plating. However, minimizing the amount of dissection required for implantation as well as lack of prominent hardware surfaces will reduce the incidence and severity of hardware related pain and correspondingly the necessity of hardware removal.

Specific Aims

1) *Prospectively establish equivalence with respect to fracture union rate after Acutrak headless compression screw fixation when compared to other fixation methods for medial malleolus fractures.*
2) *Prospectively establish equivalence with respect Patient Reported Outcome Measurement Information System (PROMIS) scores after Acutrak headless compression screw fixation when compared to other fixation methods for medial malleolus fractures.*
3) *Prospectively establish superiority with respect to hardware related pain after Acutrak headless compression screw fixation when compared to other fixation methods for medial malleolus fractures.*
4) *Prospectively establish superiority with respect to the hardware removal rate after Acutrak headless compression screw fixation when compared to other fixation methods for medial malleolus fractures.*

Study Design

Institutional Review Board and HIPAA

The institutional review boards of Stanford Hospital and Clinics and the Kaiser Permanente Hospital, South Sacramento will review and approve this study prior to initiation. All patient information will be kept confidential in accordance with HIPAA and only the study coordinator and the protocol director will have access to the data.

Inclusion/Exclusion Criteria

All ankle fractures that undergo open reduction internal fixation of the medial malleolus in adults at or over 18 years-of-age will be considered for inclusion.

We will specifically exclude pediatric ankle fractures in children under 18 years-of-age, tibial plafond (pilon) fractures in children and adults, medial malleolar osteotomies to access the talus, perform an ankle fusion, or deal with a pathologic lesion, osteonecrosis, or infection due to their diversity in diagnosis, management, and weight bearing status. Patients with prior surgical treatment of the ankle for fracture, deformity, infection, neoplasia, or other pathologic process on the ipsilateral extremity will also be excluded.

Patients that are non-weight bearing on one or both lower extremities prior to sustaining their ankle injury will be excluded.

Randomization

All elective and emergent admissions to Stanford Hospital and Clinics and Kaiser Permanente – South Sacramento that meet our inclusion/exclusion criteria will be identified and solicited for consent. Patients will be randomized by sealed envelope to surgical fixation with traditional headed screws, plates, and wires or Acutrak headless compression screws. At the time of randomization, the fracture pattern and severity, past medical history and medications, and demographic data will be documented.

Follow-up Protocol

After operative fixation, patients will receive fracture follow-up with a clinical evaluation for tenderness, radiographs to evaluate stability and union at 2 weeks, 6 weeks, 3 months of surgery and complete the PROMIS and VAS pain scores. Patients will be followed by telephonically once the fracture union is confirmed radiologically by the operating surgeon at 6 months, 1 year, and 2 years after surgical fixation. The VAS pain scores will be administered telephonically and the PROMIS questionnaires will be mailed to the patients (Table 1).[9]

Table 1: Protocol Summary

Time and Event Table	Injury/Office	2 weeks	6 weeks	3 months	6 months (over Telephone & mail)	1 year (over Telephone & mail)	2 years (over Telephone & mail)
Discuss Study	X						
Screening Log	X						
Informed Consent	X						
Eligibility Worksheet	X						
Demographic Data	X						
Medical History	X						
Randomization	X						
Clinical Assessment							
•Medial Ankle Tenderness	X	X	X	X	X	X	X
•Lateral Ankle Tenderness	X	X	X	X	X	X	X
Patient Reported Outcomes							
•PROMIS Score	X	X	X	X	X	X	X
•VAS Pain (by location)	X	X	X	X	X	X	X
•On Narcotics (yes/no)	X	X	X	X	X	X	X
Radiographs							
•Anterior-to-Posterior Ankle	X	X	X	X	-	-	-
•Lateral Ankle	X	X	X	X	-	-	-
Operative/Device	X						
Removal of Hardware		X	X	X	X	X	X
Adverse Event	X	X	X	X	X	X	X
End of Study							X

Criteria for Removal of Hardware

Hardware may be removed if there is a surgical indication or patient/surgeon preference for removal. Patients will be asked whether they feel bothersome sensitivity at the both medial and lateral malleolus. If they mention sensitivity to light touch that is not bothersome they should not be subjected to hardware removal unless by patient or surgeon preference and noted as medial or lateral hardware removed for preference. On the other hand, if they mention bothersome sensitivity, it would be rated on a 0-5 Likert intensity scale. All bothersome sensation will be subjected to hardware removal and noted as removal for sensitivity. Other reasons for hardware removal indications include infection and non-union or mal-union requiring revision open reduction and internal fixation. The location of symptoms and reason for hardware removal should be specified and documented.

Documentation of Fracture Union

Union will be defined as a pain free facture site on examination with evidence of radiographic healing and a return to full weight bearing confirmed by the operating surgeon

Power Analysis and Statistics

Retrospective review of ankle hardware removal cases indicates that 6% (8/126) of patients have their hardware removed for non-pain issues (e.g., infection, etc.) at 6 months and 17% (22/126) of patients have their hardware removed for pain on the medial or lateral side of the ankle at 6 months.[8] Hence, the overall rate of hardware removal is 24% but if we can reduce half of the medial hardware removals the overall rate would be 14.5%. To detect this 9.5% difference, it would take 424 randomized patients (alpha = 0.05, and 80% power). Medial hardware removal will be prohibited for lateral hardware pain.

Utilizing the STRIDE database available at Stanford University, there have been 155 procedures involving fixation of the medial malleolus (CPT: 27766, 27814, 27822, 27823) over the past three years. Assuming a similar procedure burden at the other major Level I Trauma center and extrapolating this three-year data, we estimate the capability to enroll 500 patients over three years.

All continuous variables will be reported as the mean and errors are reported as standard deviation. All categorical variables will be reported as the subset number and percentage of the total. Comparisons will be performed with the appropriate statistical test when indicated. Statistical significance will be set at *p* less than 0.05 with an appropriate Bonferroni correction for multiple comparisons when indicated.

Budget

The vast majority of the budget will go toward an experienced fulltime clinical research coordinator, level II (CRCII, Table 2). This person is critical to our success. Appropriately, some funds will be devoted to insuring the proper training and certification for the CRCII involved in this project as well as supply adequate computing power and meet secure data storage needs. Some funds would be used by the principal investigator and co-investigators to offset local travel and travel to national and international meetings to present the findings of this interdisciplinary work, including the American Academy of Orthopaedic Surgeons (AAOS), the Orthopaedic Trauma Association (OTA), and the American Orthopaedic Foot and Ankle Society (AOFAS).

Table 2: General Budget

Expense			**Effort**	**Cost**
Personnel	Principal Investigator	Derek F. Amanatullah	10%	$36,000/year
	Co-Investigator	Kenneth J. Hunt	3%	$10,000/year
	Co-Investigator	Julius A. Bishop	3%	$10,000/year
	Co-Investigator	Chris D. Kreulen	3%	$10,000/year
	Co-Investigator	Philip R. Wolinsky	3%	$10,000/year
	Co-Investigator	Domingo Hillare	3%	$10,000/year
	CRCII	TBD: Stanford	100%	$90,000/year

	CRCII	TBD: 3rd center	75%	$68,000/year
	CRCII	TBD: Kaiser	75%	$68,000/year
Equipment	Computers			$3,000/year
	Secure Storage			$1,000/year
Training				$5,000/year
Travel	Society Meetings			$5,000/year
	Between Sites			$5,000/year
				$275,000/year

Acumed Study Summary	
Company	Stanford University
Title	Prospective, multi-center, randomized, controlled study evaluating the union rate, rate of medial malleolus hardware removal and clinical outcomes after medial malleolus fracture fixation with Acutrak headless compression screws
Short Title	Acutrak Fixation of Medial Malleolus Fractures
Protocol Number	
Treatment Device	Acutrak headless compression screws
Control Device(s)	Mini-fragment Plating, Antiglide Plating, Headed Unicortical Screws, Headed Bicortical Screws, Tension Band Wiring
Intended Use	The Acutrak headless compression screws are intended to provide fixation and anatomically reduce fractures of the medial malleolus that occur via supination-external rotation, pronation-external rotation, or pronation-abduction resulting in an oblique fracture pattern as well as supination-adduction resulting in a vertical shear fracture pattern.
Study Purpose	The fixation provided by the Acutrak headless compression screws provide sufficient fixation to achieve union and a favorable clinical outcome in both horizontal **and** vertical medial malleolus fractures when compared to bicortical and unicortical screw fixation, tension band wiring, and mini-fragment or buttress plating. However, minimizing the amount of dissection required for implantation as well as lack of prominent hardware surfaces will reduce the incidence and severity of hardware related pain and correspondingly the necessity of hardware removal.
Study Objectives	**Primary**: • A successful outcome would be a reduction in the rate or severity of hardware related pain localized to the medial malleolus reducing the incidence of hardware removal from the medial malleolus at one year after sustaining an ankle fracture.
	Secondary: • Another successful outcome would be an equivalent radiographic and clinical union rate when compared to traditional fixation methods. • Another successful outcome would be an equivalent PROMIS scores when compared to traditional fixation methods.
	Safety Objective: • *Prospectively establish equivalence with respect to fracture union rate after Acutrak headless compression screw fixation when compared to other fixation methods for medial malleolus fractures.* • *Prospectively establish equivalence with respect to Patient Reported Outcome Measurement Information System (PROMIS) scores after Acutrak headless compression screw fixation when compared to other fixation methods for medial malleolus fractures.* • *Prospectively establish superiority with respect to hardware related pain after Acutrak headless compression screw fixation when compared to other fixation methods for medial malleolus fractures.* • *Prospectively establish superiority with respect to the hardware removal rate after Acutrak headless compression screw fixation when compared to other fixation methods for medial malleolus fractures.*

Evaluation Tools	**Subjective:** VAS Pain Score, Fracture Union **Objective:** Complications, PROMIS Scores
Subject Population	Patients sustaining a horizontal or vertical medial malleolus facture as a result of supination-external rotation, pronation-external rotation, pronation-abduction, or supination-adduction of the ankle resulting in a fracture.
Critical Eligibility Criteria	**Inclusion:** All ankle fractures that undergo open reduction internal fixation of the medial malleolus in adults at or over 18 years-of-age will be considered for inclusion.
	Exclusion: • pediatric ankle fractures • tibial plafond (pilon) fractures in children and adults • medial malleolar osteotomies to access the talus, perform an ankle fusion, or deal with a pathologic lesion, osteonecrosis, or infection • prior surgical treatment of the ankle for fracture, deformity, infection, neoplasia, or other pathologic process • non-weight bearing on one or both lower extremities prior to sustaining their ankle injury
Definition of Enrollment	Meeting Inclusion/Exclusion Criteria and Signed Informed Consent
Number of Subjects	Utilizing the STRIDE database available at Stanford University, there have been 155 procedures involving fixation of the medial malleolus (CPT: 27766, 27814, 27822, 27823) over the past three years. Assuming a similar procedure burden at another major Level I Trauma center at Kaiser Permanente Hospital, South Sacramento and extrapolating this three-year data, we estimate the capability to enroll and randomize over 500 patients requiring medial malleolus fixation over three years between the three centers.
Number of Sites	Three Level I Trauma Centers will participate: • Stanford Hospital and Clinics • Kaiser Permanente – South Sacramento • Brigham and Women's Hospital- Boston
Procedure Schedule	See Table 1
Subject Duration	The estimated duration for each subject is 2 years. Subjects are released from postoperative follow-up after post-operative observation for two years.
Study Duration	The estimated duration of the study is 5 years: 3 years for enrollment and 2 year for postoperative follow-up for each enrolled subject.
Safety	All adverse events and complications will be continuously monitored throughout the study. The type and frequency will be analyzed by a medical monitor.
Statistical Methods	All continuous variables will be reported as the mean and errors are reported as standard deviation. All categorical variables will be reported as the subset number and percentage of the total. Comparisons will be performed with the appropriate statistical test when indicated. Statistical significance will be set at p less than 0.05 with an appropriate Bonferroni correction for multiple comparisons when indicated.

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