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TITLE: The Comparative Efficacy of the Masquelet versus Titanium Mesh Cage Reconstruction Techniques for the Treatment of Large Long Bone Deficiencies

PRINCIPAL INVESTIGATORS: Zbigniew Gugala, MD,PhD

CONTRACTING ORGANIZATION: The University of Texas Medical Branch
Galveston, TX 77555

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6. AUTHOR(S)
Zbigniew Gugala, MD,PhD
Ronald W. Lindsey, MD

E-Mail: zgugala@utmb.edu; rlindsey@utmb.edu

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The University of Texas Medical Branch
2.316 Rebecca Sealy Hospital
301 University Blvd
Galveston, TX 77555-0165

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

The study comprises a single center, randomized, two-arm clinical trial conducted at the Department of Orthopaedic Surgery & Rehabilitation, University of Texas Medical Branch, Galveston, TX, with a primary objective to assess and compare the functional outcome of patients with large segmental bone defects reconstructed with the Masquelet technique (MT) versus the titanium mesh cage technique (TMCT). The secondary objectives include the radiographic determination of defect healing, and comparative assessment of cost and resource expenditures between the two techniques. From 24 patients with segmental defects presented to our institution throughout the entire trial period, 16 met the study eligibility criteria and were successfully enrolled, and they include 9 MT, 7 TMCT. Within the last 12-month study period, 1 patient completed the study, 9 are actively participating, and 1 was withdrawn. The withdrawn subject was a patient (study subject #10) from the TMCT group who experienced an adverse event comprising an infection requiring hospitalization, cage removal, and local (ie, beads) and systemic antibiotic therapy. The infection was successfully treated, but patients was removed from participation in the trial as per the protocol. So far, 9 study subjects (5 MT, 4 TMCT) are being actively followed, and their study courses are uneventful. There is 1 potentially eligible study patient identified. The trial is ongoing and patient enrollment is in progress.

15. SUBJECT TERMS
Segmental bone defects reconstruction; Masquelet technique; Titanium mesh cage technique

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1. Introduction

The United States Department of Defense funds a clinical trial that can be a major improvement in the treatment of extremity trauma associated with segmental bone defects. These devastating injuries occur in both civilians and the military population. They typically result from motor vehicle accidents, high-energy fractures, gunshot injuries, and blast injuries, but also can be an outcome of iatrogenic segmental bone resections due to infection or tumor. Despite many recent advances in this area, achieving healing bone defect and restoring injured limb function has been extremely challenging. Standard treatment options are exceedingly complex, require highly specialized equipment and/or skills, and typically necessitate multiple surgical procedures over a protracted period of time. Furthermore, major complications frequently occur with all the standard options and return to acceptable limb function is typically rare, and, in many instances amputation is required.

The present clinical study addresses this issue by assessing and comparing two innovative surgical bone defect treatment techniques that can be significantly more effective than the standard treatment options for civilian and military patients with these conditions. One treatment method—the Masquelet technique—involves two-stage surgery. In the first stage, a biomembrane around the defect is induced by the application of a cement spacer. The secondstage surgery is performed 6-8 weeks later and consists of cement spacer removal and bone graft placement while preserving the biomembrane. The other method—the cage technique—has been developed by the study principal investigators (PIs), and comprises one-stage surgical procedure in which a cylindrical, fenestrated titanium cage is packed with bone graft and implanted in the defect. Initial clinical experience with both of these techniques has been very promising, and there have been no prospective clinical studies comparing these two novel defect treatment methods. The present study aims to address that void.

The study is a randomized two-arm, single-center clinical trial conducted at the Department of Orthopaedic Surgery and Rehabilitation, The University of Texas Medical Branch (UTMB) in Galveston, Texas. The trial's primary objective is to assess and compare the functional outcomes of patients with large segmental bone defects reconstructed with the Masquelet technique versus the cage technique. The trial's secondary objectives include the radiographic determination of defect healing and the comparative assessment of cost and resource expenditures between the two techniques.

2. Keywords

Critical-size bone defects;
Segmental bone defect reconstruction;
Masquelet technique;
Titanium mesh cage technique

3. Overall Project Summary

Study Continuation and Approvals/Amendments: The annual approval for continuation of clinical trial has been obtained from the UTMB Institutional Review Board (IRB) on Mar 11, 2017. No time lapses occurred between the renewed IRB approvals.

There were no amendments filed to the approved protocol of the trial.

The study is currently ongoing. No deviations from the protocol have been noted.

The study has been granted 1-year no-cost extension by DoD until Sep 30, 2018.

There has been a single adverse event encountered.

Adverse Event (Subject #10):

There was 1 adverse events (AE) that occurred since the last annual report.

Subject ID 10/03/2016 was consented for participation in the study and randomized to the cage trial arm on 3/29/2016. He had his index surgery on 4/1/2016. His followups were uneventful. On 12/7/2016 he presents to the clinic and describes a foul smelling odor from left tibial surgical site. On investigation of surgical defect by the study Co-I, it was noticed that the patient had drainage from the wound requiring frequently changing dressings. On examination, subject had no fever, left lower extremity motor function grossly intact, sensation intact to light touch in deep peroneal, superficial peroneal, tibial, sural, and saphenous distributions. There were palpable pedal pulses. A 5x3 cm wound opening over the left anteromedial tibia with exposed hardware and bone and positive foul odor present as well. No gross purulence at surgical site. Subject was admitted and underwent surgical exploration. During surgery necrotic and contaminated tissue structures were seen, tibial debridement and jet lavage using saline washout was performed to cleanse the surgical site after removal of the tibial hardware (including the cage). The bone defect was packed with antibiotic beads. On 12/13/2016, a wound vacuum/negative pressure device was placed to drain the surgical site and enhance would healing. Subject was discharged from hospital. The nature of this AE met the exclusion criteria to continue the study, and subsequently the subject was removed from study participation

The current status of the study:

A total of 16 patients have been enrolled in the study, of which 3 were withdrawn (subjects #2, #3, and #4) as reported in the previous annual reports, and also 1 (subject #10) was withdrawn since the last report due to AEs (as indicated above). Within the last 12-month period, 1 study subject uneventfully reached the 18-month study followup, and thereby met the terms for study completion. The table below depicts current patient participation in the trial to date:

Trial Arm	Total Trial Subjects Enrolled	Subjects Completed Trial Uneventfully	Subjects Actively Participating	Subjects Removed from Trial Continuation
Masquelet	9	3	5	1
Cage	7	0	4	3
Total:	**16**	**3**	**9**	**4**

Within the last 12-month period encompassing the present annual report, 1 patient completed the study, and 9 patients continue follow-up. As previously stated, there was 1 AE, and it resulted in study discontinuation. All other study subjects are being followed uneventfully as per their respective remaining study follow-ups, ie 12 months, and 18 months.

Patient Enrollment and Follow-up:

Overall, patient enrollment in the trial has plateaued. No new subjects have been enrolled since last report. Over the last 12-month period, a total of 3 patients with segmental defects presented to our institution. Among these patients 2 were civilian prisoners who met the study clinical eligibility criteria but could not be enrolled because PI's institutional IRB disapproved participation of this vulnerable population; the other patient was a free-world patient with segmental defect; he will be reviewed for study eligibility and approached for study participation. Nine previously enrolled patients are currently being followed up as per the study protocol. The 1 patient who successfully completed the trial is:

Trial Patient #6: A 73-year-old male with distal right tibial shaft fracture nonunion after a motor vehicle collision. He had undergone open reduction and internal fixation of his tibia at another hospital prior to presenting to our trauma center. The patient met study inclusion criteria, signed informed consent, and was randomized to the 2-stage Masquelet trial arm. In the 1-stage of Masquelet reconstruction, the right tibia hardware was removed, I&D of tibial segmental defect performed, and an interopositional antibiotic cement spacer placed in the defect. The subsequent 2-stage consisted of the index defect reconstruction procedure in combination with the allograft per the protocol in the index procedure. The patient has completed all required study visits and reached the study endpoint without any adverse events. The patient has shown successful functional outcomes after treatment.

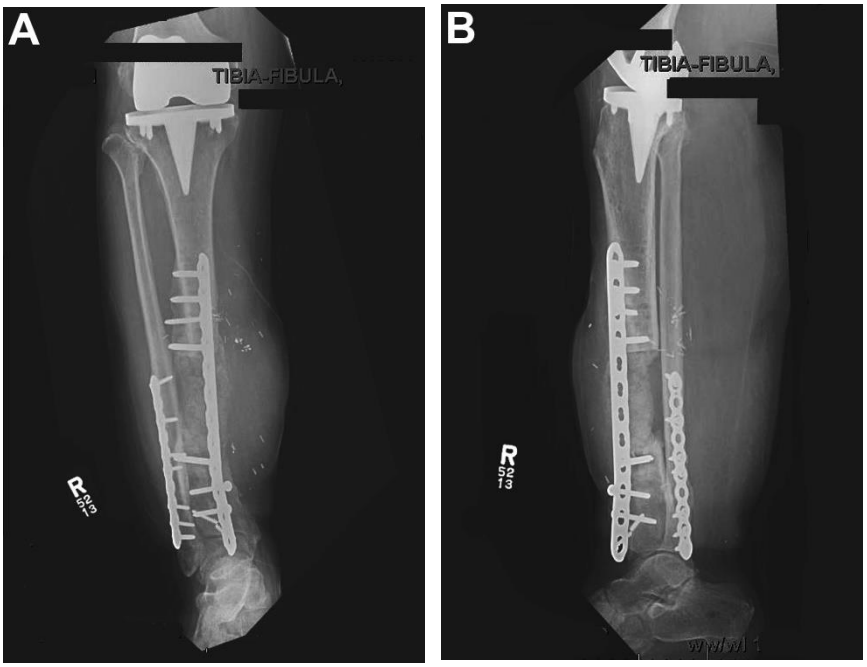

Fig 1. A motor vehicle accident led to right distal tibia-fibula facture which was initially treated with ORIF. An infected nonunion developed. After excision of the infected bone, the resultant segmental defect was treated using 2-stage Masquelet technique in combination with allograft and plate-screw stabilization. The defect healing progressed uneventfully and graft consolidation was evident at 18 months post-surgical radiography (A,B).

Enhancement of Study Enrollment:

The study PIs have identified 1 potentially eligible patient who is currently treated for chronic infection/osteomyelitis. This patient will be approached for study participation, and is expected to y be enrolled pending meeting study inclusion/exclusion criteria.

Eligible patient identification and enrollment for the trial are ongoing; however, they progresses slower than anticipated. The PIs are actively soliciting referrals of the eligible patients from UTMB satellite out- and inpatient clinic locations.

4. Key Research Accomplishments

The clinical trial is ongoing.
UTMB IRB approvals/renewals have been obtained for study continuation.
The trial is conducted in accordance with the IRB-approved protocol, and the trial progresses uneventfully since the last annual report.
The trial period has been extended until Sep 30, 2018 (no cost extension granted by DoD).

5. Conclusion

Study enrollment remains slow. Improving patient accrual is an imperative, and can be achived by enhancing referrals of eligible patients from the UTMB main and satellite clinic sites. The study has enrolled 16 patients to date, of whom 3 successfully finished the trial, 4 were withdrawn, and 10 are actively participating. No new subject have been enrolled sing the last report. The followup of all trial patients in progressing uneventfully. No study protocol deviations have occurred. There has been 1 adverse event encountered which has resulted in withdrawal from the study. The patients who completed the study are satisfied with the outcome. To reduce the incidence of AEs, the PIs very critically review each eligible patient for compliance—this, however, compromises the enrollment.

Initial radiographic and functional outcomes of limb/defect healing for patients treated with both the Masquelet (Arm I) and the cage (Arm II) techniques are encouraging; however, the Masquelet appears to perform better than the cage.

Utilizing the UTMB's EPIC electronic medical records facilitates planning the patients' followup clinic visits, informing/reminding the enrolled patients about the study participation and filling out the questionnaires. Using recently adopted the reloadable ClinCard reimbursement system streamlines and simplifies the process of patient reimbursement for study participation and compliance with the timeframe of the followup visits.

6. Publications, Abstracts, and Presentations

Lindsey RW, Gugala Z. The Comparative Efficacy of the Masquelet Technique versus Titanium Mesh Cage Technique in the Reconstruction of Segmental Bone Defects. A DoD-UTMB Clinical Trial. Baylor College of Medicine Grand Rounds, Houston, TX, on Oct 10, 2014.

Lindsey RW, Gugala Z. A DoD-UTMB Clinical Trial Determining the Efficacy of the Masquelet Technique versus Titanium Mesh Cage Technique in the Reconstruction of Segmental Bone Defects. UTMB Monthly Conference, Victory Lakes, TX, on Jan 21, 2015.

Lindsey RW. Managing post-traumatic femoral bone defects. The UCSF Annual International Orthopaedic Trauma Course. San Francisco, CA. April 28, 2016.

Lindsey RW, Gugala Z. New Horizons: Experience with the Bone Cage. The 26th Annual Meeting of the Baltimore Limb Deformity Course: Masters of Disaster Managing Osteomyelitis in the 21st Century. Baltimore, MD. August 25, 2016.

Lindsey RW. Titanium Cages: How We Can Enhance Their Success. The Annual Meeting of the Orthopaedic Trauma Association. National Harbor, MD. October 5-8, 2016.

7. Inventions, Patents and Licenses

Nothing to report.

8. Reportable Outcomes

Nothing to report.

9. Other Achievements

Nothing to report.

10. References

Nothing to report.

11. Appendices

Nothing to report.