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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

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14. ABSTRACT The study comprises a single center, randomized, two-arm clinical trial conducted at the Department of Orthopaedic Surgery & Rehabilitation, The University of Texas Medical Branch at Galveston, Texas, with a primary objective to assess and compare the functional outcomes of patients with large segmental bone defects reconstructed with the Masquelet technique (MT) versus the titanium mesh cage technique (TMCT) in combination with bone grating. The secondary objectives include the radiographic determination of defect healing, and comparative assessment of cost and resource expenditures between the two techniques. From 25 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 encompassing this report, 2 patients completed the study (1 MT and 1 TMCT), and 7 patients are still participating. These 7 study participating subjects (4 MT, 3 TMCT) are being followed, and their study courses are uneventful. There was 1 potentially eligible study patient identified, however, ultimately, he was concluded not meeting the study inclusion criteria. The trial is ongoing and patient enrollment is still in progress.					
15. SUBJECT TERMS Critical-size bone defects; Segmental bone defect reconstruction; Masquelet technique; Titanium mesh cage technique; Bone grafting.					
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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 of bone defect and restoring injured limb function have been extremely challenging. Standard treatment options are prolonged, complex, or require highly specialized equipment and/or skills. Furthermore, they typically necessitate multiple surgical procedures over a protracted period of time. Hence, major complications frequently occur with the standard options, and return to acceptable limb function is typically rare, and, in many instances, amputation is required.

The present clinical trial 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. One treatment method—the Masquelet technique—involves two-stage surgery. In the first stage, a cement spacer is applied within the defect, and as a result, a biomembrane develops spontaneously around the defect. This biomembrane is highly vascularized and rich in growth factors—it serves as a biological enclosure for subsequently applied bone graft. The second stage, is performed 6-8 weeks later, and consists of cement spacer removal while preserving the biomembrane, and tightly packing bone graft within the defect surrounded by the biomembrane. The second defect treatment method—the cage technique—was developed by the study principal investigators (PIs) and it comprises one-stage surgical procedure. In this single stage defect recantation, a cylindrical, fenestrated titanium cage is tightly packed with bone graft, and such construct is placed within the defect. Compared to the biomembrane, the cage similarly encloses bone graft, offers sound biomechanical stimulation of the graft within the defect, albeit it lacks the respective biological characteristics of the biomembrane. Hence, both the biomembrane and the cage exhibit distinctive biological and biomechanical properties which can provide unique milieu for bone graft reconstitution and subsequently defect healing. The current literature suggests that the Masquelet technique can potentially be very effective to achieve bone defect healing; also, our clinical experience with the cage technique has been very favorable. However, there have been any clinical studies to compare these two defect reconstructive techniques. The present prospective clinical trial assessing and comparing the clinical efficacies of these two novel defect treatment methods aims to address that void.

The study is a single-center, randomized, two-arm, clinical trial conducted in the Department of Orthopaedic Surgery and Rehabilitation, The University of Texas Medical Branch (UTMB) at Galveston, Texas. The trial's primary objective is to assess and compare the functional outcomes of patients with large segmental bone defects of various etiologies reconstructed with the Masquelet technique versus the titanium mesh cage technique, both in combination with bone grafting. The trial's secondary objectives include the radiographic (biplanar radiography, CT) 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;
Bone grafting.

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 Jan 26, 2018.

No time lapses occurred between the renewed IRB approvals.

The study is currently ongoing.

No amendments were filed to the approved trial protocol.

No deviations or violations of the approved trial protocol have occurred.

No adverse events were encountered since the last annual report.

The study has recently been granted the second 1-year no-cost extension by DoD until Sep 29, 2019.

The current status of the study:

A total of 16 patients have been enrolled in the study, of which 4 were withdrawn (subjects #2, #3, #4, and #10) as reported in the previous annual reports. Within the last 12-month period, 2 study subjects 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	4	4	1
Cage	7	1	3	3
Total:	16	5	7	4

Within the last 12-month period encompassing the present annual report, 2 patients completed the study, and 7 patients continue follow-up, and no new patients have been enrolled. Subjects #8, and #9 did not show up for their 1-year follow-up, despite numerous attempts to contact them. The study personnel will continue to contact these patients; if unsuccessful, these patients will be removed within 2 months. All other study subjects are being followed as per their respective study timepoints, 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 2 patients with segmental bone defects presented to our institution. Among these patients 1 was civilian prisoners who 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, but he ultimately did not meet the study eligibility criteria. Seven previously enrolled patients currently remain in the study and are being followed up as per the study protocol. Below are examples of two patients representing both the cage and the Masquelet study arms who successfully completed the trial:

Cage Arm Patient: A 59-year-old male presented with infected nonunion in the tibia as a result of open fracture. The patient was enrolled into the study and randomized to the cage technique (Arm II) for defect reconstruction in combination with allograft-DBM graft. The patient completed all study follow-up visits (2w, 6w, 3m, 6m, 12m, 18m). He demonstrated uneventful defect healing as evidenced by plain radiography, computed tomography, and subjective functional assessment.

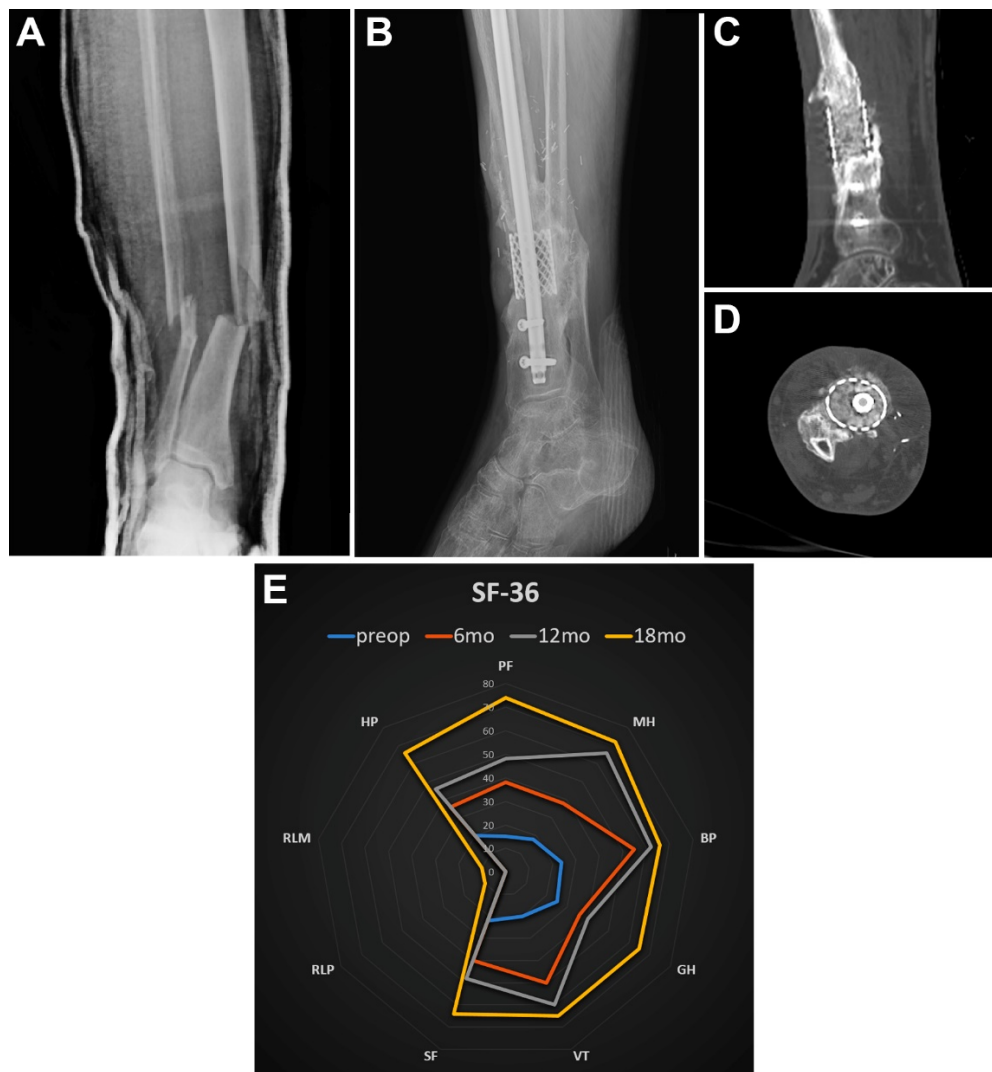


Fig 1. A chronic infected nonunion following Grade IIIB open tibia fracture (A). The excised infected bone produced segmental defect treated with a cylindrical titanium cage in combination with allograft-DBM, and an intramedullary nail stabilization. The defect healing progressed uneventfully to union as indicated by plane radiography at 18 months (B). CT imaging depicted new bone within and outside the cage (C,D). The patient's functional outcome as per SF36 has progressively improved throughout the followup reaching an excellent result (E).

Masquelet Arm Patient: A 73-year-old male with a chronic infected nonunion/defect in the tibial middiaphysis was enrolled to the study and randomized to the Masquelet technique (Arm I). The patient received the two-stage Masquelet reconstructive surgery for bone defect in combination with allograft cancellous croutons-DBM composite. The decision was made not to use RIA graft harvesting (typical for Masquelet technique) from the femur because of an ipsilateral knee prosthesis present in the operated extremity. The patient completed all study followup visits (2w, 6w, 3m, 6m, 12m, and 18m). The patient demonstrated uneventful defect healing with very good radiographic (plane radiography and CT) and subjective functional outcomes (SF36).

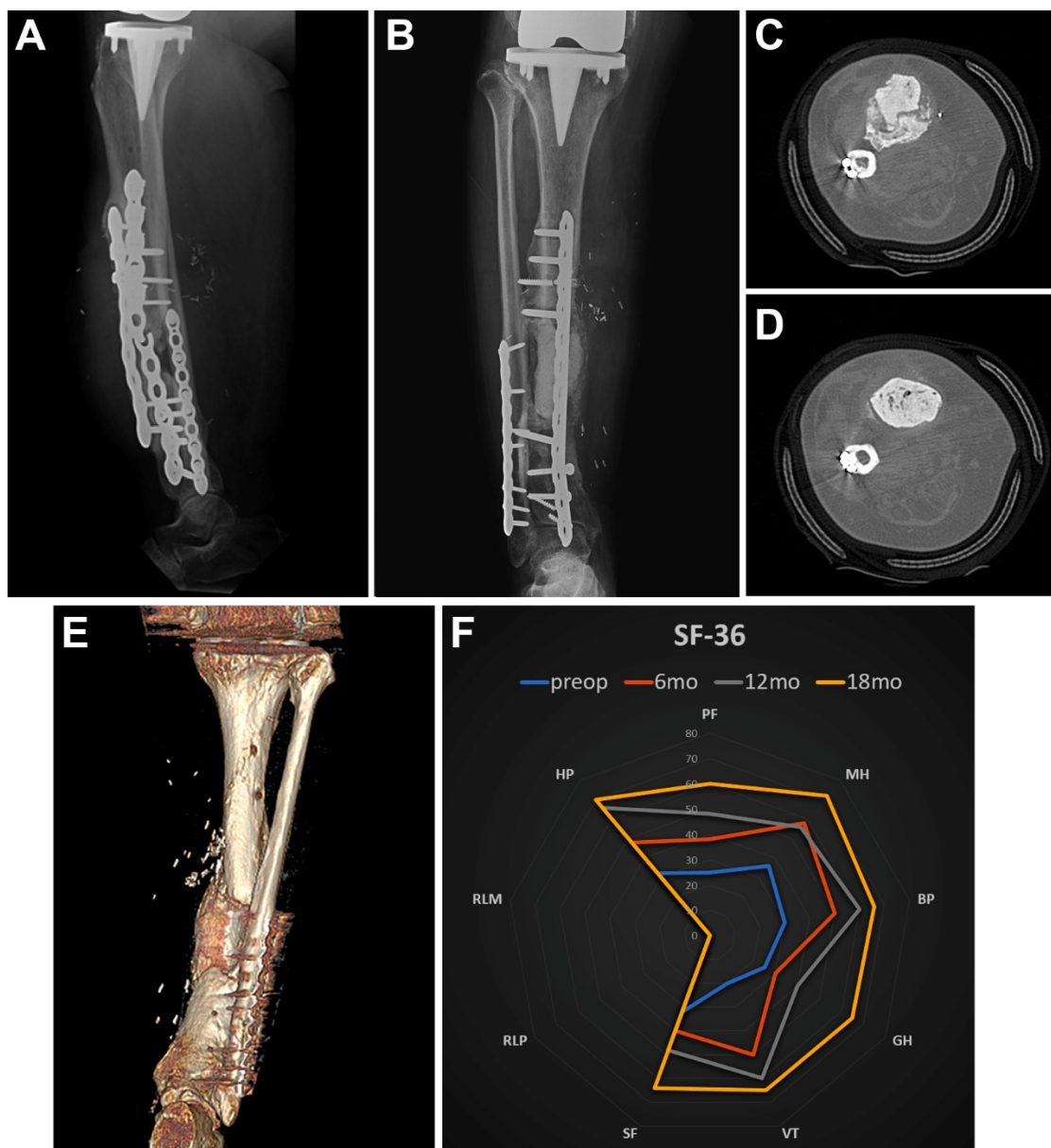


Fig 2. A tibial mid-diaphyseal infected nonunion with hardware failure (A) was treated with two-stage Masquelet technique combined with allograft cancellous-DBM graft, and locking plate-screw stabilization. The graft consolidation was evident on plane radiography (B), cross-sectional CT images (C,D), and three-dimensional CT reconstruction (E). Progressive increase in overall subjective functional outcome was apparent as indicated by the scores obtained from SF36 (F).

Enhancement of Study Enrollment:

Eligible patient identification and enrollment for the trial are ongoing; however, they progress 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.

There were no protocol deviations, violations, or adverse events since the last annual report.

The trial period has been extended until Sep 29, 2019 by granting no cost extension by DoD.

5. Conclusion

Study enrollment plateaued. Improving patient accrual is an imperative, and can be potentially achieved by enhancing referrals of eligible patients from the UTMB main and satellite clinic sites. The recent improvement in trauma care, advent of effective guidelines for antibiotic therapy and wound management (negative-pressure WoundVac) have resulted in lowering the numbers of the patients presenting with infected nonunions requiring iatrogenic bone resections. This significantly impacted the enrollment of the study eligible patients.

The study has reviewed 25 patients presented to UTMB as potentially eligible, from that group 16 patients were enrolled to date, of whom 5 successfully finished the trial, 4 were withdrawn, and 7 are actively participating. No new subjects have been enrolled since the last annual report. The followup of participating patients is progressing uneventfully. No study protocol deviation or violations have occurred. All study regulatory approvals have been timely obtained without any approval lapses. All patients who completed the study are satisfied with the outcome.

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 reconstruction technique appears to perform better than the cage. This is a preliminary observation; a thorough comparative analysis of the patients' outcomes in both trial arms will be performed for the final report.

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 enhances compliance with timely 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.