Management of Traumatic Bone Defects in Tibial Plateau Fractures with Antibiotic-Impregnated Biodegradable Calcium Sulfate Beads: A Prospective Clinical Trial

Principal Investigator / Sponsor:	Ross Leighton M.D.
Other Investigators:	Canadian Orthopaedic Trauma Society
Research Coordinators:	Kelly Trask Shelley MacDonald
Funder:	Biocomposites, Ltd.
Clinical Trial Registration:	NCT02456194

Version 2, 2017/03/31

Introduction / Background

The tibial plateau is the flattened surface of the top of the tibia bone, which makes it part of the knee joint. It is covered with cartilage, which is critical for the smooth movement of the knee joint. It also houses the menisci ("shock absorbers") of the knee joint and a number of ligaments that act to stabilize the knee joint. Fractures of this bone are difficult to manage since they can disrupt these soft tissues in addition to the bone. Fractures are classified according to their severity. The most common classification of tibial plateau fractures is by Schatzker (Figure 1), with the classification number increasing with severity[1].

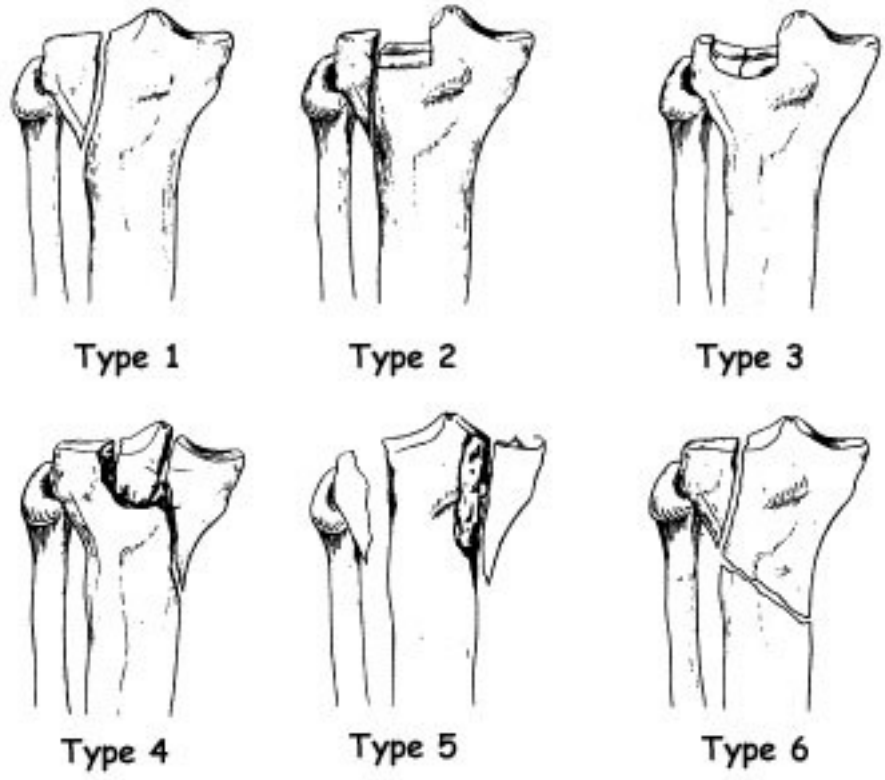

Figure 1: Schatzker Classification of Tibial Plateau Fractures

Tibial plateau fractures require anatomical reduction of the joint surface and stable fixation to allow early range of motion and progressive weight bearing to facilitate healing[2]. If the tibial plateau fracture involves a depression of the joint surface, elevating the fracture fragment can result in a defect, or void, in the metaphyseal bone. Standard practice is to fill this void with bone graft or a bone graft substitute. Autogenous Iliac Bone Grafting (AIBG) has long been considered the gold standard in subarticular bone defect management in conjunction with conventional open reduction and internal fixation techniques for unstable tibial plateau fractures[3]

although complications of graft harvest, ranging from temporary pain and numbness to long-term functional impairment, are well documented[4-8]. These complications, along with the limited availability of AIBG, have led to the development of bone graft substitutes.

Calcium sulfate has been used as a bone substitute for nearly 100 years. It is low cost, readily available, has a structure similar to bone allowing for osteoconductivity, and it has a proven safety record. Calcium sulfate can also be used for local antibiotic delivery for the treatment or prevention of infection[9].

Advances in trauma care have reduced infection rates in tibial plateau fractures from 80%[10] to 10 – 14% [11], but the complex nature of the injury has been shown to be an independent risk factor for infection[12]. Preventing colonization of the bone graft used in tibial plateau fractures is desirable. The ability to provide antibiotics locally, rather than systemically, for the duration of the graft remodeling may improve outcomes of this injury if bony healing is not compromised.

We propose a prospective clinical trial of tibial plateau fractures treated with internal fixation and a calcium sulfate graft which can be mixed with antibiotics and molded into various bead sizes for implantation into bone defects. The graft material chosen for this study is STIMULAN Rapid Cure (Biocomposites, UK), which is approved for use as a bone void filler and may be mixed with a variety of antibiotics. The combination of STIMULAN + antibiotic in bead form is herein referred to as the "study device".

Why is a Trial Needed Now?

While studies have been done to look at prevention and treatment of infection with the study device[13-25], there is no published evidence of its effectiveness in acute, closed, non-infected tibial plateau fractures. Previous studies have indicated that calcium sulfate is resorbed by three months after implantation and that bone has remodeled by six months[26-27]. These studies did not include the use of antibiotics in the calcium sulfate.

Study Aims

Our primary study aim is to look at resorption and remodeling of the study device into bone. Another important aim of the study is to look at subsidence, or collapse, of the joint surface. Secondary outcomes are those that are clinically important after this injury including time to bone healing, knee range of motion, knee stability, return to work and activities, infection, wound problems, functional outcomes, and complications.

How Will the Results of This Trial Be Used?

This trial will provide clinical evidence on the use of antibiotics mixed with calcium sulfate in the treatment of acute, closed, non-infected tibial plateau fractures. This will guide orthopaedic surgeons in their clinical decision making for this complex injury.

Methods

This will be a prospective, non-randomized study. Up to four centers in Canada with extensive experience in the treatment of tibial plateau fractures will be selected for this multi-centre study. The study will be an investigator-driven study with QEII Health Sciences Centre as the lead site. It will be supported by an unrestricted research grant from Biocomposites Ltd. with the funds being distributed to all sites via the lead site. Thirty (30) consecutive patients who meet the inclusion criteria will be recruited for the study and followed for one year.

Inclusion Criteria:

Patient selection criteria will include:

- Adult (skeletally mature) men or women;
- Acute, closed, tibial plateau fractures, Schatzker grade 1 through 5;
- Internal fixation and use of study device per protocol;
- Fracture repair within 30 days of injury;
- Signed informed consent to participate in study.

Exclusion Criteria:

- Uncontrolled diabetes;
- Severe degenerative or metabolic bone disease;
- Malignancy;
- Severe vascular or neurologic disease;
- Alcoholism;
- Substance abuse;
- Use of systemic steroids;
- Immunosuppressive therapy;
- Hypercalcaemia;
- Renal-compromised patients;
- Osteomyelitis or chronic infection in the study limb;
- Women who are pregnant or breast-feeding.

All sites will obtain approval from the institutional review board at their respective hospitals and participants will be required to provide informed consent prior to any study procedures. Since the study device is an option for treatment of this injury, informed consent may occur post-operatively if the study device was used per protocol as the standard of care. Patients who consent to participate in study but do not receive the study device will not be considered study participants.

All visits required will be those as per regular follow up visits in their institutions, so no travel expenses should be required. If however extra visits are required for study purposes (e.g. CT scan performed after hours), a small stipend will be paid to cover parking/ travel.

Standard open reduction and internal fixation techniques will be used to restore fracture stability. The implants utilized for this purpose will include locked and unlocked premolded proximal tibial plates and small fragment plates as per the decision of the attending surgeon. Subarticular grafting with the study device will be accomplished via an open procedure. The study device cannot be used alone or with screws only, it must be used with standard internal fixation as noted above.

Preparation of the Study Device

The study device is to be prepared with the antibiotic chosen according to the manufacturer's mixing guidelines (Appendix A). The selection of antibiotic from those in the mixing guidelines is left to the surgeon's discretion. A maximum of one 10cc kit of STIMULAN Rapid Cure per participant is to be used. The STIMULAN is to be prepared in bead form. The selection of bead size is at the discretion of the surgeon.

Post-operative immobilization, weight-bearing, and rehabilitation protocol will be the standard of care for each surgeon.

Follow-up will be scheduled at 6 weeks, 3 months, 6 months, and 12 months as per the usual at each site. Other visits may be "clinically indicated" but would not be required as a part of this study. Baseline information will be collected during the initial hospital stay.

Risks and Benefits of Study Participation

This trial does not involve any experimental devices or procedures. The risks of participating are no greater than standard of care. As with any study, there is a risk of breach of confidentiality. There is no direct benefit to participants in this study. The results of this study will benefit future patients with this injury by providing more evidence on treatment with the study device.

How Will The Outcome Measures Be Measured at Follow-up?

Basic demographic information: At the time of study inclusion, information on basic demographics (age, sex), past medical history, co-morbidities, medications (i.e. bisphosphonates, vitamin D), pre-injury level of activity and/or employment and mechanism of injury will be collected for all participants.

Functional outcomes: The Knee injury Osteoarthritis Outcome Score (KOOS)[28] is a validated self-administered questionnaire which will be completed at the designated follow-up visits. The questionnaire completion time is approximately 15 minutes. Return to work and return to pre-injury activities will be measured in weeks.

Clinical outcome: Range of motion will be evaluated and will include active and passive flexion and extension. Knee stability will be assessed. The surgical site will be examined for progression in healing, wound issues (drainage, dehiscence, etc.) or signs of infection.

Radiological outcome: Evaluation will be performed at each participating centre and all radiographs will be sent to the principal investigation centre with all identifiers removed. Exams at each study visit will be the standard AP and lateral radiographs. Amount of study device remaining and percent remodeled will be measured on plain radiographs. Time to union will be defined as bridging callus evident on two x-rays. Our previous study on tibial plateau fractures indicated that subsidence occurs between three and six months after surgery[29]. Therefore, at six months a CT scan will be performed to determine if any study device remains and to measure any subsidence of the joint surface.

Adverse Events: Since the study device is being used according to the indications for use, monitoring of adverse events will be according to standard clinical practice. Reporting of serious adverse events will be according to the REB policy at participating sites, with copies sent to the lead site and the Quality Department at Biocomposites. Adverse events of interest in the study are those associated with the surgical procedure and healing of the injury.

Data Collection, Management, and Retention

Each study participant will be assigned a unique Subject ID to safeguard confidentiality. The Subject ID will be used on all data collection forms. Subject IDs will be assigned consecutively at each site. Participating sites will be provided with a site number and all the required Case Report Forms prior to initiation. Completed CRFs and questionnaires from each study site will be sent via Fax or e-mail to the lead site after each patient follow-up visit, according to the data transfer and/or sub-site agreement in effect. Sites will also be given the option to enter de-identified data directly into REDCap. Study sites will keep the originals and file them in the subject binder at each site. Radiographic images (x-rays and CT) for each subject will be de-identified and copied onto a compact disc (CD) and submitted to the lead site at the end of the study. See Appendix B for schedule of events.

Data management will be coordinated from the lead site (QEII Health Sciences Centre). Study data will be managed using REDCap electronic data capture tools hosted by Nova Scotia Health Authority. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. Sites will be given a choice to either continue to send CRF's to the lead site or they will be given dedicated login information and training on how to access the REDCap tool and enter data directly into REDCap.

Study documents will be retained for seven (7) years. Sites will store and maintain all study-related documents according to local policies, guidelines, and standards. Destruction of study records will be in accordance with local policies.

Analysis of Results

All analysis will be performed at the lead site. Descriptive statistics will be used to describe the study sample. Patients will be evaluated as to union, subsidence, loss of graft or premature resorption, percent of graft remaining at each visit, knee range of motion, knee stability, loss of fixation or fixation failure, infection, functional recovery (outcome scores and return to work, return to activity) and effect of tobacco use, age, sex, fracture classification. The sample size of thirty participants was chosen based on the expected recruitment rate at this site and others planning to participate in the interest of providing objective evidence of the healing potential with this device in patients with this injury.

References

1. Schatzker J, McBroom R, Bruce D. (1979). The tibial plateau fracture. The Toronto experience 1968--1975. *Clin Orthop Relat Res.* Jan-Feb 138:94-104.
2. Koval KJ, Helfet DL. (1995). Tibial plateau fractures: evaluation and treatment. *J Am Acad Orthop Surg.* 3:86-94.
3. Segal, D., A. V. Franchi, et al. (1985). "Iliac autograft for reconstruction of severely depressed fracture of a lateral tibial plateau. Brief note." *J Bone Joint Surg Am* 67(8): 1270-2.
4. Younger, E., Chapman, MW (1989). "Morbidity at bone graft donor sites." *J. Orthop Trauma* 3: 192-195.
5. Goulet, J. A., L. E. Senunas, et al. (1997). "Autogenous iliac crest bone graft. Complications and functional assessment." *Clin Orthop* (339): 76-81.
6. Fowler, B. L., B. E. Dall, et al. (1995). "Complications associated with harvesting autogenous iliac bone graft." *Am J Orthop* 24(12): 895-903.
7. Seiler, J. G., 3rd and J. Johnson (2000). "Iliac crest autogenous bone grafting: donor site complications." *J South Orthop Assoc* 9(2): 91-7.
8. St John, T. A., A. R. Vaccaro, et al. (2003). "Physical and monetary costs associated with autogenous bone graft harvesting." *Am J Orthop* 32(1):18-23.
9. Beuerlein MJ, McKee MD. (2010). Calcium sulfates: what is the evidence? *J Orthop Trauma.* 24 Suppl 1:S46-51.
10. Young MJ, Barrack RL. (1994). Complications of internal fixation of tibial plateau fractures. *Orthop Rev.* 23:149–154.
11. Berkson EM, Virkus WW. (2006). High-Energy Tibial Plateau Fractures. *J Am Acad Orthop Surg.* Jan 14(1):20–31.
12. Bachoura A, Guitton TG, Smith RM, Vrahas MS, Zurakowski D, Ring D. Infirmity and Injury Complexity are Risk Factors for Surgical-site Infection after Operative Fracture Care. *Clin Orthop Relat Res*. 2010 Dec 16; DOI: 10.1007/s11999-010-1737-2.
13. Gauland C. Managing lower-extremity osteomyelitis locally with surgical debridement and synthetic calcium sulfate antibiotic tablets. *Adv Skin Wound Care*. 2011;24(11):515-523.
14. Lei D, Zhanzhong M, Huaikuo Y, Lei X, Gongbo Y. (2012). Chapter 10: Bone Grafting. Zorzi A (Eds), Treatment of chronic osteomyelitis using vancomycin-impregnated calcium sulphate cement (pp. 147-156). DOI: 10.5772/1450
15. McPherson EJ, Dipane MV, Sherif SM. (2013). Dissolvable antibiotic beads in treatment of periprosthetic joint infection and revision arthroplasty. The use of synthetic pure calcium sulphate (Stimulan) impregnated with vancomycin & tobramycin. *Joint Implant Surgery & Research Foundation*, 3(1):32-43.
16. Burrow JD, Lopez MJ, Pereira GC, Robbins MA, Geissler T. (2013). The use of pure synthetic calcium sulphate (Stimulan) as a bioabsorbable antibiotic delivery vehicle in hip and knee arthroplasty. *Joint Implant Surgery & Research Foundation*, 3(3):28-29.

17. Kallala R, Nizam I, Haddad F. (2013, October). *Outcomes following use of antibiotic-eluting, absorbable, calcium sulphate beads in revision hip and knee surgery for periprosthetic infection.* Poster presented at the International Society for Technology in Arthroplasty 26th Annual Congress, Palm Beach, Florida, USA.
18. Nayar D, Duffy P, Aldridge C, Longstaff L, Shaw N, Scott S. (2013, September). *Experience with antibiotic impregnated dissolvable synthetic pure calcium sulphate beads in infected bone and joints – A case series*. Poster presented 32nd European Bone and Joint Infection Society Conference, Prague, Czech Republic.
19. Saghieh S, Murtada A, Sheikh Taha AM, Masrouha K. (2011). Treatment of infected non-union of the long bones with calcium sulphate pellets impregnated with antibiotics. *Eurpoean Cells and Materials*, 21(2):26.
20. Maale GE, Eager J. (2012, February). *Local elution profiles of a synthesized CaSO4 pellet, loaded with vancomycin and tobramycin for infected total joints*. Paper presented at the American Academy of Orthopaedic Surgeons, San Francisco, CA, USA.
21. Swords K, Martinez DR, Lockhart JL, Carrion R. A preliminary report on the usage of an intracorporal antibiotic cast with synthetic high purity CaSO4 for the treatment of infected penile implant. *J Sex Med*. 2013;10(4):1162-1169.
22. Roche AJ, Selvaratnam V, Mukhopadhava S, Unnikrishnan N, Abiddin Z, Narayan B, Giotakis N, Anig H, Nayagam S. (2011). Antibiotic impregnated bioabsorbable carriers for treatment of chronic intramedullary osteomyelitis. *Abstracts / Injury Extra*. 42:95-169.
23. Whitlark JD, Rotondo LD, Su A. (2013, August). *Management of below the knee amputation (BKA) stump breakdown using antibiotic-loaded synthetic calcium sulfate beads: A case series.* Presentation and Abstracts Musculoskeletal Infection Society, Philadelphia, PA, USA.
24. Parihar M, Ahuja D. (2012). Infected non-union of radius and ulna – Strategy of approach. *Journal of Orthopaedic Case Reports,* 2(4):26-31.
25. Papagelopoulos PJ, Mavrogenis AF, Tsiodras S, Vlastou C, Giamarellou H, Soucacos PN. Calcium sulphate delivery system with tobramycin for the treatment of chronic calcaneal osteomyelitis. *J Int Med Res*. 2006;34(6):704-712.
26. Kelly CM, Wilkins RM, Gitellis S, et al. The use of a surgical grade calcium sulfate as a bone graft substitute. Results of a multicenter trial. *Clin Orthop Relat Res*. 2001; 382:42-50.
27. Yu HK, Ma H, Zhang C, Su J, Zhao J, Li J, Bai Y, Tang H. Treatment of tibial plateau fractures with high strength injectable calcium sulphate. *Int Orthop*. 2009 Aug;33(4):1127-33.
28. Roos EM, Lohmander LS. Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. *Health Qual Life Outcomes* 2003;1:64
29. Russell TA, Leighton RK. Comparison of autogenous bone graft and endothermic calcium phosphate cement for defect augmentation in tibial plateau fractures. A

multicenter, prospective, randomized study. *J Bone Joint Surg Am*. 2008; 90(10):2057-61.

APPENDIX A

STIMULAN Antibiotic Mixing Guidelines (Stimulan Rapid Cure Instructions for Use)

APPENDIX B

Schedule of Events

	Baseline	6 weeks	3 months	6 months	12 months
Informed Consent	**X**				
Clinic Visit and CRF Completion	**X**	**X**	**X**	**X**	**X**
Range of Motion		**X**	**X**	**X**	**X**
KOOS questionnaire	**X**	**X**	**X**	**X**	**X**
Assess for Adverse Events	**X**	**X**	**X**	**X**	**X**
X-ray (AP & lat)	**X**	**X**	**X**	**X**	**X**
CT scan				**X**	