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RESEARCH ARTICLE

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

Ross Leighton, MD, FRCSC, FACS[1]*, Rashed Alqudhaya, MD[1], Michael Forsythe, MD[2], G. Yves Laflamme, MD[3], Andrew Furey, MD[4], Prism Schneider, MD, PhD[5], Job Doornberg, MD, PhD[6], Jaarsma, Ruurd, M.D. PhD[7]

[1]Nova Scotia Health Authority Suite 4875
[2]Horizon Health Network
[3]Hôpital du Sacré-Coeur de Montréal
[4]Faculty of Medicine/Surgery, Health Sciences Centre
[5]Foothills Medical Centre - McCaig Tower
[6]University of Amsterdam, Groningen.GR
[7]Finders Medical Center (Level 5)

*leightonr2@gmail.com

ABSTRACT

Objectives: The purpose of this study was to assess adverse events and resorption of antibiotic-impregnated calcium sulfate beads used as a nonstructural void filler in tibia plateau fractures. This device may be more adaptable to a specific bacterium than vancomycin powder as it allows the mixtures of specific bactericidal antibiotics to treat bacterium with specific sensitivities.

Design: A multicenter, non-randomized, uncontrolled prospective cohort study.

Setting: Five level 1 trauma centers.

Participants: Thirty adults with an acute closed tibia plateau fracture, OTA 41B and 41C fractures, requiring operative fixation.

Intervention: After fracture fixation, the subchondral bone void was filled with the study device.

Main Outcome Measures: Local wound reaction to the device was assessed and resorption of the calcium sulfate was measured on serial x-rays. Follow-up assessments occurred at six weeks, three months, six months and one year, with a CT scan performed at six months to determine resorption of the device.

Results: Thirteen male and 17 female participants were recruited with a mean age of 53.3 ± 12.8 years. The median age was 55 years with a range of 29 to 78 years of age. Two participants reported serous drainage: one resolved without treatment, the other was diagnosed as a deep infection and required plate removal and oral antibiotics. There were no local or systemic allergic reactions. Resorption of the material averaged 70% by three months, 87% at six months, and 100% at one year.

Conclusions: This device performed as anticipated and completely resorbed without any unexpected adverse events. It allowed for personalizing antibiotic choice with better reported elutional characteristics than vancomycin powder over two weeks and six weeks. Surgical site drainage was low, and 97% union rate was achieved. This is a safe surgical augment for local release of a chosen antibiotic into a contained subchondral defect in a periarticular fracture.

Introduction

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[1]. This was altered with level I evidence by Russel at al in 200 which illustrated that calcium phosphate performed better than AIBG by reducing early and late subsidence. Complications of graft harvest, ranging from temporary pain and numbness to long-term functional impairment, are well documented[2-6]. These complications, along with the limited availability of AIBG in elderly patients, have led to the development of bone graft substitutes, such as calcium sulfate and calcium phosphate. Calcium phosphate has proven superior to autograft in providing support to the subchondral bone: Trenholm's biomechanical study as a precursor to this clinical study was compelling evidence that autograft or autograft provided minimal support to the subchondral collapsed segment[7, 8]. Most calcium phosphate devices have not been FDA or Health Canada approved for the addition of antibiotics Plus, their release of the antibiotics is very slow relative to calcium sulfate[9,10]. Stimulan is approved in Canada but not in the USA as an antibiotic depo device.

Calcium sulfate has been used as a bone substitute for nearly 100 years[11,12]. It is low cost, readily available, has a structure similar to bone allowing for absorption and replacement with bone, and it has a proven safety record. Calcium sulfate can also be used for local antibiotic delivery for the treatment or prevention of infection[13]. Calcium sulfate is not as supportive as calcium phosphate, so the internal fixation construct must be substantial enough to elevate and support the subchondral reconstruction.

In the past, the use of calcium sulfate in periarticular defects has led to increased wound drainage and periarticular cyst formation[15]. The improvement in the production of calcium sulfate and the proposed reduction of impurities has been proposed by industry to provide potential improvements in its acceptability to the patient and the surgeon. This paper will determine if these new claims are indeed true. This study does not compare IV antibiotic use to treatment with antibiotic impregnated calcium sulfate. This study was a pilot study to determine if calcium sulfate was indeed safe for use in patients with the usual risk for infection with a closed fracture. The surgeons and REB board felt the potential reduced risk of infection would outweigh a substantive risk to the patient of superinfections occurring in this well-studied group.

Advances in trauma care have reduced infection rates in tibia plateau fractures from 80%[16] to 10 – 14%[17], but the complex nature of the injury has been shown to be an independent risk factor for infection[18]. Preventing colonization of the bone graft or bone graft substitute used in tibia plateau fractures is desirable. The ability to provide antibiotics locally, rather than systemically, for the duration of the graft remodeling could marginally improve outcomes of this injury, if bony healing is not compromised by the substitute. This was not the primary reason for this pilot study but could be a secondary outcome.

This prospective clinical trial of tibia plateau fractures treated with internal fixation and STIMULAN Rapid Cure produced by Biocomposites, in the United Kingdom, mixed

with antibiotics was designed to evaluate absorption and remodeling of the STIMULAN while observing the normal expected bone healing. Additional outcomes include subsidence of the joint surface, time to bone healing, range of motion of the knee, return to work and activities, infection, wound problems, functional outcomes, and complications. While prior studies have evaluated prevention and treatment of infection with the study device[19-33], there is no published evidence of its performance and or its effectiveness in acute, closed, tibial plateau fractures. Previous studies have indicated that calcium sulfate is absorbed by three months after implantation and that bone has remodeled by six months[34, 35]. These studies did not include the use of antibiotics in the calcium sulfate; therefore, it is unknown whether the inclusion of antibiotics will affect, wound drainage, absorption of the device or bone remodeling. Calcium sulfate is approved as an antibiotic delivery device in Canada, but is not FDA approved for this purpose at this time. At this time, the use of the study device in this manner would be off label in the USA. This study was not done to determine which patient population would benefit from the device but to determine if wound drainage, bone healing and device resorption would occur normally and as expected in a closed tibia plateau fracture. Is the device safe to use in patients with a significant fracture in an area such as the tibia plateau, without a large soft tissue envelope where surgical wound drainage can be relatively common.

If this study indicates no major complications associated with the STIMULAN device, the results of this pilot study will be utilized to design a large randomized trial looking at the added value of STIMULAN to the present standard of care in the treatment of a well-documented deep infection.

A secondary literature evaluation of the elution characteristic of antibiotic impregnated Stimulan versus the elution characteristics of vancomycin powder was also performed. This comparison may allow the best product to be chosen for each surgical situation by the surgeon or infectious disease team.

Methods

Participating Sites

This prospective, non-randomized study involved five sites in Canada with extensive experience in the treatment of tibia plateau fractures. The five sites came on at staggered times, with all five sites involved for the last year of the study. The study was approved by each local Research Ethics Board at all participating institutions and was registered at ClinicalTrials.gov with the registration number NCT02456194. Informed consent was obtained from all participants prior to proceeding with the study procedure.

Participants

Eligible participants were prospectively enrolled between September 2015 and January 2018, according to the following inclusion criteria: adults with acute, closed, tibial plateau fractures, Schatzker Type I through V as well as the OTA/AO classification, 41-B3 through 41-C2. Internal fixation was utilized plus the use of the study device as per the protocol; definitive fracture repair within 30 days of injury; and signed informed consent to participate in study. The exclusion criteria were: uncontrolled diabetes; severe degenerative or metabolic bone disease; malignancy; severe vascular or

neurologic disease; alcoholism; substance abuse; use of systemic steroids; immunosuppressive therapy; hypercalcemia; renal-compromised patients; osteomyelitis or chronic infection in the study limb; and women who are pregnant or breast-feeding. Over 100 patients were screened to recruit our 30 participants. The main deterrent to participation was the long term follow up required necessitating additional clinic attendance.

The participants were followed for one year with serial clinical and radiographic follow-up. A CT scan was performed at six months to provide an accurate assessment of resorption of the device. Scheduled follow-ups were at six weeks, three months, six months, and one year. Baseline information and questionnaires were collected during the initial hospital stay.

Surgical Procedure and Post-operative Protocol

Standard open reduction and internal fixation techniques were used to restore fracture stability. The implants utilized for this purpose included locked and unlocked pre-contoured proximal tibial plates and small fragment plates at the discretion of the attending surgeon. Subchondral grafting in the metaphysis with the study device was accomplished via an open procedure. The device was gently packed into the metaphyseal bone, the plate was applied and the screws were placed through the bone and the device, as required.

The study device was prepared in bead form and mixed with one or two antibiotics, according to the manufacturer's Instructions For Use. The selection of antibiotics from those in the Instructions For Use was left to the treating surgeon's discretion. A maximum of one 10cc kit of STIMULAN Rapid Cure was used per participant and the volume was recorded. The size of bead could also be selected by the surgeon to match the anatomic area and the size of the defect.

Post-operative immobilization, weight bearing, and rehabilitation protocol were at the discretion of each treating surgeon and the patient.

Radiographic Outcomes

Anteroposterior and lateral radiographs were examined at each follow-up to determine fracture healing, presence of graft device, subsidence or collapse of the joint surface, varus/valgus tilt, and heterotopic ossification. There was an independent orthopedic surgeon, not involved in the study, to look at any complications and outcomes. The CT scan at six months was used to determine the amount of graft device that remained visible as was performed in Russell's study and would allow comparisons to that literature. The healing of the fracture was followed very closely to determine if the device in any way inhibited fracture union.

Clinical and Functional Outcomes

Local wound reaction to the device was assessed by recording redness, swelling, and presence of serous drainage. The clinical and functional outcomes included return to work and return to regular activities, range of motion and stability of the knee, weight bearing status, the Knee injury Osteoarthritis Outcome Score, KOOS, wound healing concerns, and reported complications.[36]

Data Management

Study data were collected at each site by trained research staff. The data were entered

and managed using REDCap electronic data capture tools hosted at the local Health Authority[37]. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies. All radiographs and CT scans were transferred to the lead site for evaluation by a single orthopaedic surgeon who was independent of the study. All participants in the study were assigned a 4-digit study identification number. No personal information on individual participants was transmitted. All data were stored securely in accordance with applicable laws and regulations governing the protection of personal information and personal health information.

Results

Thirty participants who met all of the inclusion criteria and none of the exclusion criteria were enrolled in the study, 13 males and 17 females. The median age was 55 with a range from 29 to 78 years old, with a mean and standard deviation of 53.3 ± 12.8 years. Average body mass index was 29.4 ± 8.7 (median, 27 [range 18-55.2]). There were five current and seven past smokers. Ten participants were employed in active jobs, six in sedentary jobs, and the remainder were not working or retired at the time of injury. Falls were the most common mechanism of injury (Table 1). There were 17 Schatzker II fractures, OTA/AO 41-B3.1; two Schatzker III, OTA/AO 41-B3.2; three Schatzker IV, OTA/AO 41-C1; and eight Schatzker V, OTA/AO 41-C2 fractures. Twenty-nine participants completed follow-up. One participant did not return for the 12-month visit and we were unable to contact the patient, but the fracture had healed and there were no reported adverse events at the six-month visit. This was treated as an intent to treat with one missing data point.

Table 1: Mechanism of Injury

Mechanism of Injury	Number (%)
Fall from height	8 (27%)
Fall from standing	6 (20%)
Motorcycle/ All terrain / Snowmobile Accident	4 (13%)
Motor Vehicle Accident (driver/passenger)	3 (10%)
Motor Vehicle Accident (pedestrian/cyclist)	3 (10%)
Skiing	3 (10%)
Other	2 (7%)
Direct Trauma	1 (3%)

The average length of surgery was one hour and 46 minutes. The median time was1 hour 29 minutes and ranged from 39 minutes to four hours and four minutes). The antibiotics chosen to be mixed with the STIMULAN beads are shown in Table 2. The average defect size was 7.1 ± 8.9 cc and the average amount of STIMULAN Rapid Cure used was 53.6% ± 35.1% of the kit. Twenty-four participants were fixed with a single plate; all but one was locking compression plates. Multiple plates, up to three or four plates, were used in the remaining six

participants. The resistance to joint compression is primarily with the mode of fixation, i.e. rafting of the screws below the subchondral bone. All devices used may indeed add to this fixation and thus combine to form a full construct fixation. However, if not fixed well with the plates and screw implants the devices will not reduce joint depression in and of themselves and only add marginally at best to the whole construct.

Table 2: Antibiotics Used

Antibiotics	Number (%)
Vancomycin	11 (37%)
Tobramycin	7 (23%)
Gentamicin	6 (20%)
Gentamicin & Vancomycin	4 (13%)
Vancomycin & Tobramycin	2 (7%)

All participants healed their fracture, but some did require additional surgical procedures. One participant was diagnosed with a deep infection and required surgical debridement and oral antibiotic management. One patient rapidly developed traumatic arthritis and underwent a total knee replacement,TKR, within 18 months of the initial fracture.

Radiographic Results

All but one participant had healed without subchondral or chondral collapse by the 12-month visit as defined by radiographic healing. That participant had healed their fracture by three months but developed gross valgus deformity with traumatic arthritis by six months following the initial fracture and was revised to a TKR at nine months and went on to heal uneventfully. In total, 76.7% were completely healed by three months and 83.3% were healed by six months. Only 13.3% of participants showed 2 mm or more of subsidence of the joint surface (Figure 1). This example fracture was not elevated as high as possible leaving the knee in slight valgus. This subsidence occurred early in the healing process, as it was evident on the six-week x-rays. It was the determination of the committee that this was a mechanical failure secondary to malreduction and low position of the rafting of screws, not the STIMULAN study device. Subsidence was measured as a comparison to the literature on similar devices such as the studies on calcium phosphate versus iliac crest bone graft. Unfortunately we did not use radiographic balls to assess magnification this will be used in the planned randomized prospective multicenter study. The radiographic outcomes and clinical outcomes were similar to the published literature. No increased wound drainage was appreciated in this cohort of patients.

Seventy percent of participants had no STIMULAN visible on x-ray at three months. This increased to 87% at six months and 100% at 12 months. The device did not impair fracture healing from the expected normal, as reported in other studies[7, 38, 39]. Based on the absorption and bone healing, it satisfied the basis for being osteopromotive, meaning it does not inhibit bone healing.

Figure 1: Valgus malreduction of the fracture plus early subsidence of the joint surface: intraoperative (a) and six months (b).

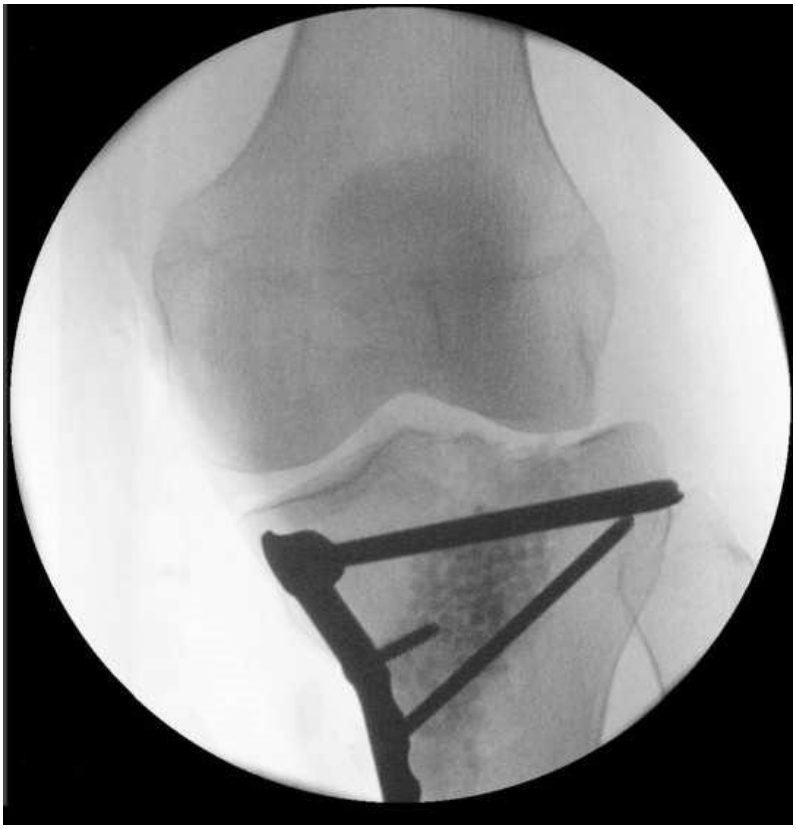


Figure 1a

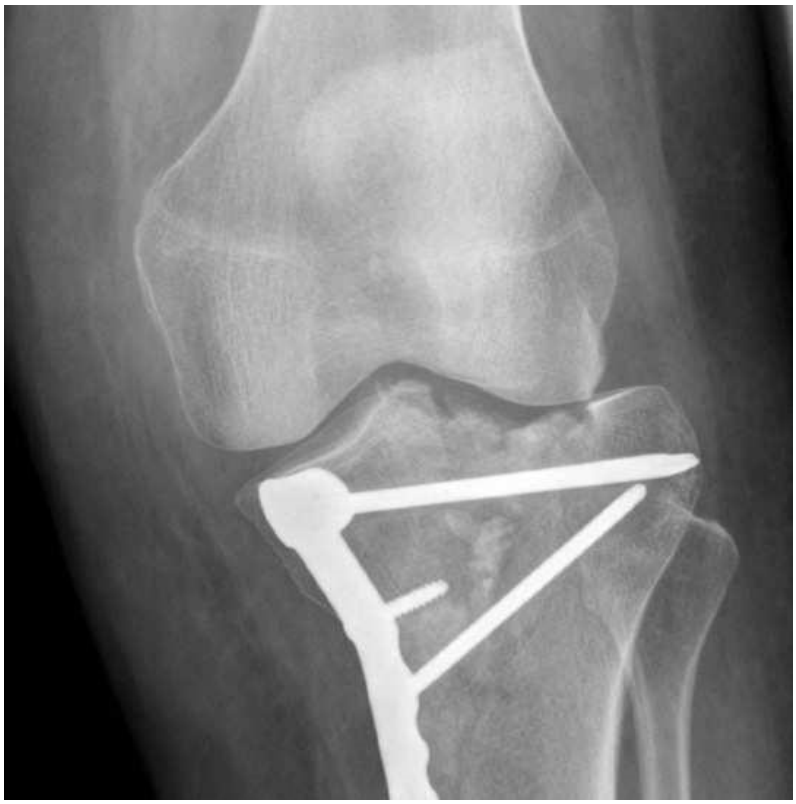


Figure 1b

Clinical and Functional Outcomes

The KOOS was administered at baseline and each follow-up. The KOOS consists of five subscales; Pain, other Symptoms, Activities of Daily Living (ADL), Sport and Recreation Function (Sport/Rec) and knee-related Quality of Life (QOL). A normalized score is calculated for each subscale with 100 indicating no symptoms and 0 indicating extreme symptoms. The KOOS outcomes are shown in Figure 2.

Figure 2: Knee injury Osteoarthritis Outcome Score (KOOS) Subscales: "Pain" (a); other "Symptoms" (b); Activities of Daily Living, "ADL" (c); Sport and Recreation Function, "Sport/Rec" (d); and knee-related Quality of Life, "QOL" (e).

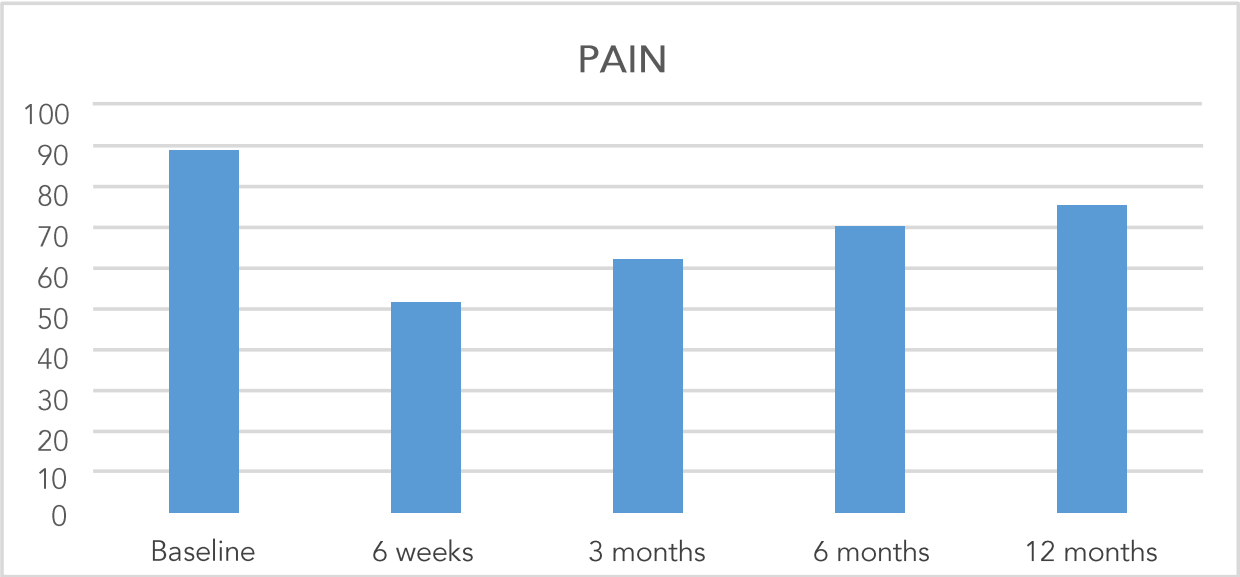


Figure 2a

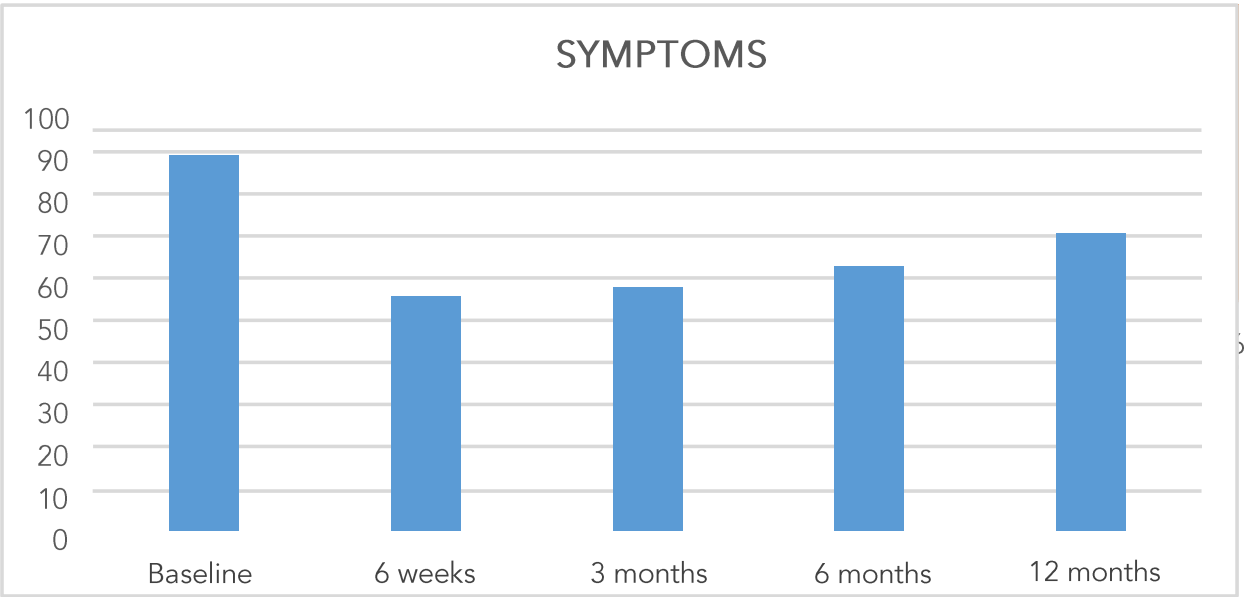


Figure 2b

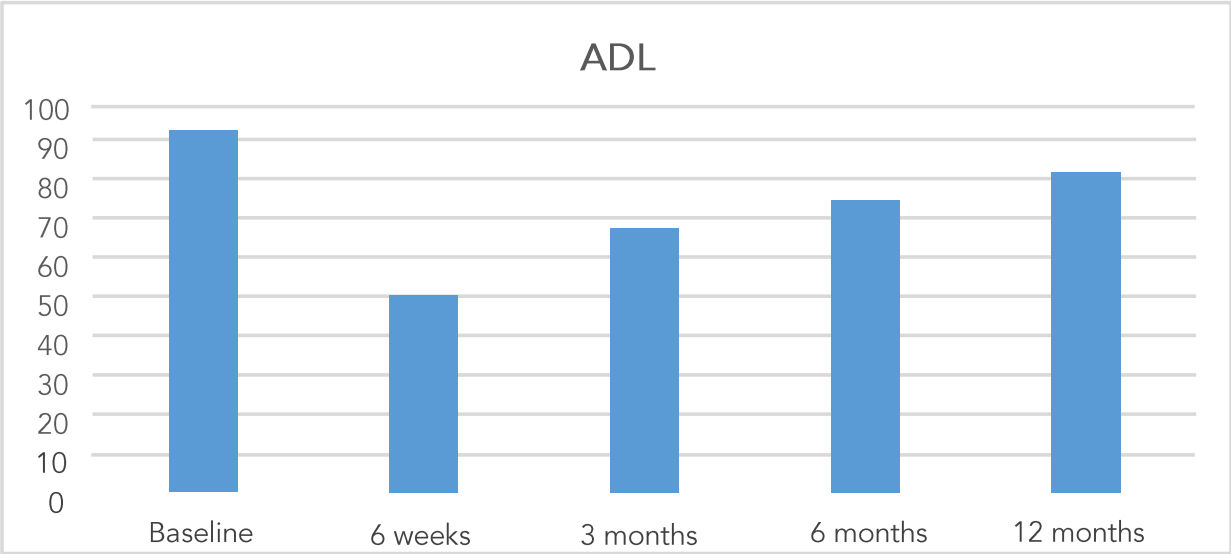


Figure 2c

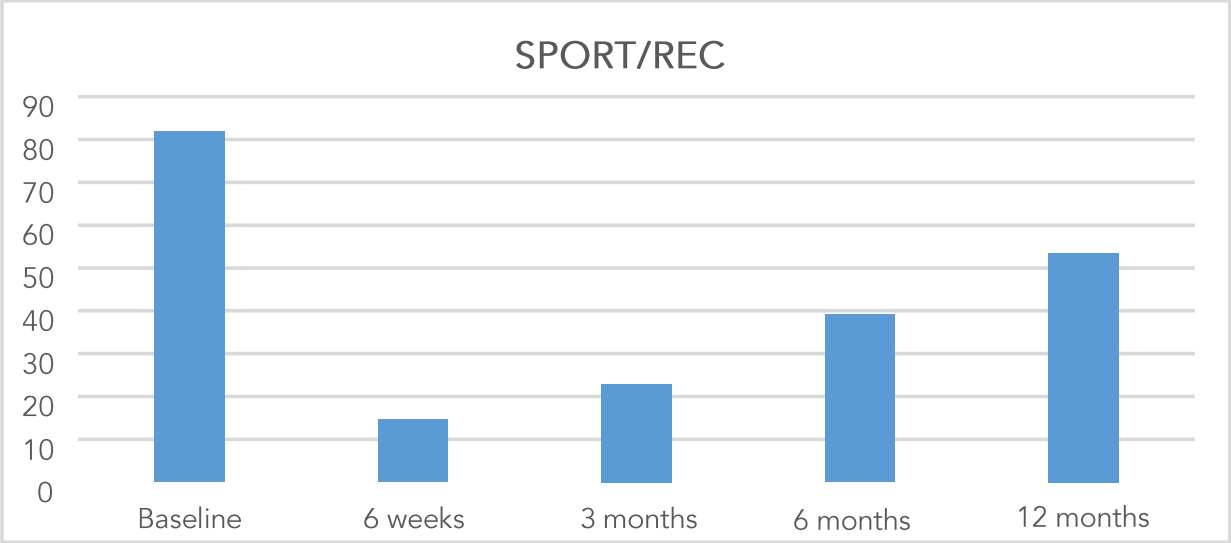


Figure 2d

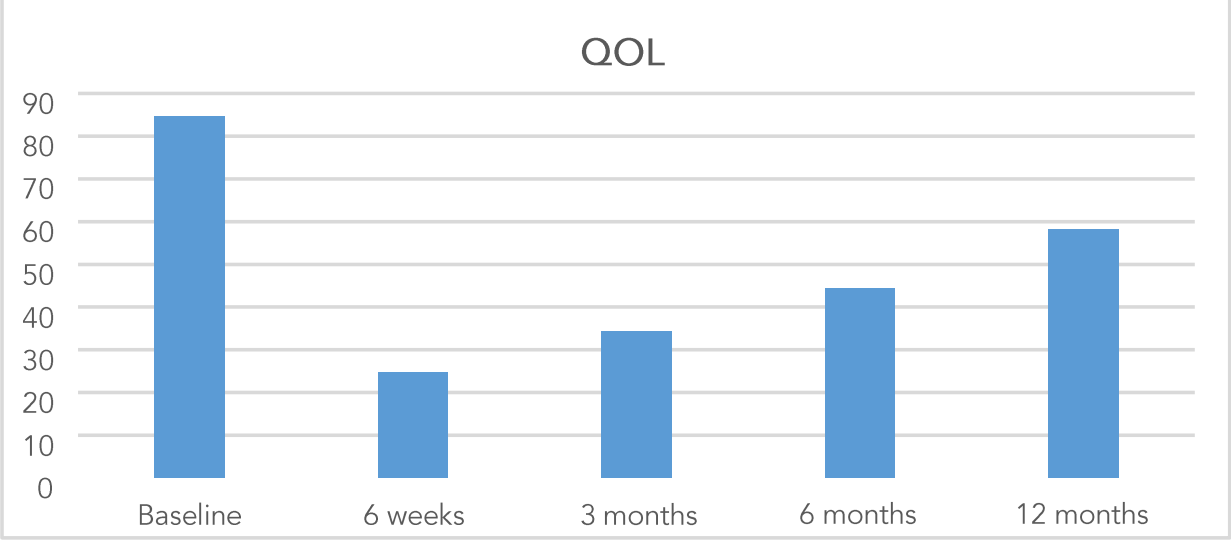


Figure 2e

Range of motion of the knee increased at each follow-up with a mean flexion at six weeks of 97.4 ± 27.4 degrees, 108.5 ± 25.4 degrees at three months, 121.2 ± 20 degrees at six months, and 126.5 ± 11.9 degrees at one year. By one year, all but one participant had achieved at least 90% of the ROM of their uninjured knee.

Seventeen participants, 56.7%, were non-weight bearing for at least six weeks. By three months 25 participants, 83.3%, were weight bearing as tolerated or full weight bearing. All participants were full weight bearing at 6 months. The one patient requiring the TKR was full weight bearing but required a TKR to treat his pain and deformity.

Twelve of sixteen participants who were employed at the time of injury had returned to full duties by six months. Only 13 participants reported having returned to their pre-injury level of activity at 12 months. This is consistent with the recent orthopedic literature and pain literature[40].

Complications

Postoperative swelling and redness were within normal limits. There was no unacceptable wound drainage, as would have been seen with previous calcium sulfate formulations. One participant reported serous drainage that resolved without treatment. One obese participant presented with serous drainage secondary to what was initially felt to be a stitch abscess, which settled very quickly with local wound care. However, this progressed to a deep infection and at nine months required removal of the plate and screws and serial irrigation and debridement with long-term oral antibiotics. This resolved relatively quickly once the plate was removed on the second of two surgeries No specific removal of the calcium sulfate was required as has been reported with calcium phosphate. One participant became infected with staphylococcus aureus of a previous external fixator pin site. This was treated with oral antibiotics and resolved without any further surgeries.

There was one report of an unusual complication of intraarticular heterotopic bone requiring arthroscopic debridement. The committee could not relate this to the operative treatment or the study device and it is very rare in the literature for this injury. Three participants experienced hardware irritation. One was revised to a smaller plate at three months. Another complained of pain with physiotherapy after the fracture healed and had the plate and screws removed at seven months. The third, described above, was revised to a total knee replacement after early collapse of the lateral chondral surface. None of these were deemed by independent evaluation to be related to the study device. These would have happened with any bone void augment. They were secondary to the initial injury, fixation construct, bone factors, chondral injury, and normal recovery from a tibia plateau fracture.

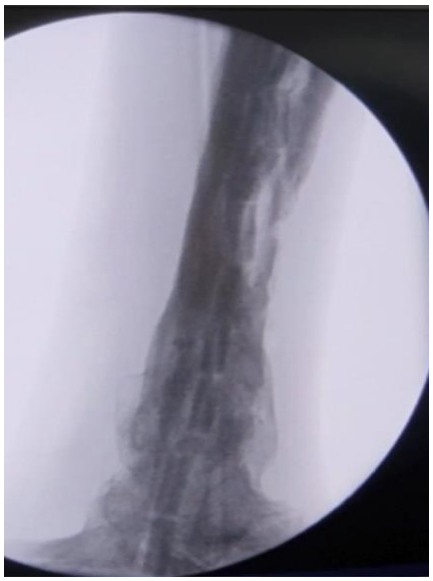
Discussion

Calcium sulfate, in previous forms, created major issues when used in acute periarticular fractures, with multiple studies showing large cyst formation and lack of bone healing, particularly in defects contiguous with joints and synovial fluid. Many indicated a decreased healing of the defects and others actually showed larger defects after absorption of the device. This new more purified form of calcium sulfate, although providing no indication of

bone induction, did not inhibit normal bone healing, and no subchondral cysts were seen. It did not create any defects in a well-vascularized void and resorbed as anticipated and was replaced with bone. Mixture of this device with various carefully selected antibiotics and combinations of antibiotics, based on anatomic site and on cultures when possible, was performed without any mixing issues. The hardening time for the beads was not always the same, as outlined by the manufacturer, and depended on the mixture of antibiotics chosen by the surgeon.

An advantage of this device is that one can mix it early in the case and leave it to harden in the sterile field to be used when required during the procedure. The size of the device can also be determined by the surgeon. Smaller beads will resorb more quickly due to a higher surface area. This allows for a higher MIC level to be present but it would last a shorter period of time. This device also come as a "bullet" that can allow the surgeon to place it down a femoral or tibia canal to treat infection within the long bone. (Figure 3) This device is much more adaptable to the treatment of a specific infection as the device can be mixed with any antibiotic which can be chosen based on the usual or specific sensitivities of the bacterium isolated in the wound. The device also has the advantage of different sized beads that can be created by the surgeon to address different bone void characteristics. The device can be drilled and screws can pass through the device without harm but the STIMULAN does not necessarily add to the fixation construct initially but is osteoconductive and allows bone ingrowth into the defect. The mechanical construct prevents subsidence, not the calcium sulphate. Fixation must be obtained in the usual way with rafting of the screws in the subchondral bone and fixation in the opposite metaphysis via a precontoured plate. Collapse of the subchondral bone is usually due to chondral damage, traumatic apoptosis, and / or suboptimal subchondral support via the chosen construct. Figures 1 and 4 illustrate both of this type of failure.

Figure 3—Tibia canal implanted with Stimulan Bullets to treat an intramedullary infection



Distal Tibia canal with Bullets in the canal for infected TFCC nail

Calcium sulfate appears to be an effective bone void filler in subchondral tibia defects, while also allowing antibiotic elution into the bone and surrounding soft tissue[10, 21]. This could be an excellent choice for patients at high risk for infection. When one compares to the vancomycin powder literature, it would suggest this device to be much more adaptable to the patient's bacteria, as opposed to hoping that vancomycin will cover the assumed bacteria and potentially allow gram negative bacteria to be preselected for growth[41]

In general, there is a lack of significant high-quality evidence supporting the use of vancomycin powder and clinical studies have produced conflicting results[42-45]. Johnson et al looked at serum and wound concentrations after intra-wound administration of vancomycin powder in total joint arthroplasty and found that with a half-life of 7.2 hours, virtually all vancomycin was gone in 36 hours (five half-lives)[46]. In vitro elution characteristics of STIMULAN show high concentrations of any antibiotic chosen in STIMULAN for a four to six weeks extended time period and lower concentrations for up to 12 weeks[21]. Calcium sulfate is reported to elute antibiotics over a longer duration of time than vancomycin powder, with a higher sustained level of antibiotic locally[9, 10].

The device was osteoconductive, as it did not appear to impede bone healing and indeed allowed bone voids to fill rapidly. The subsidence rate was acceptable at 13% (4 participants). Russell et al reported-on subsidence of tibia plateau fractures in their trial comparing autograft to calcium phosphate bone substitute and found a 30% rate of late subsidence in the autograft group, using a 2 mm step as the minimum to be clinically significant. This compared very unfavorably with only a 9% subsidence rate in the bone substitute group [7]. In our study, the subsidence occurred early in the healing process. STIMULAN is not intended to provide structural support; however, it would appear that it is at least equal to autograft when compared to the literature. This is not a direct study comparison; therefore, we cannot state that it is any better than bone graft based on this study alone. Subsidence of 2 mm is an arbitrary number and its clinical significance is probably clinically meaningful for medial plateau injuries, but may not be clinically significant for the lateral plateau. Many have suggested clinical significance may not be reached until the subsidence is more than 5 mm in a lateral plateau injury[47].

There was one deep infection in our cohort in a morbidly obese, BMI>50, diabetic participant who was noncompliant with follow-up appointments or taking prescribed antibiotics for the infection following diagnosis. This participant's infection was resolved following irrigation and debridement plus removal of the plate and screw fixation, but without excision of the study device. This is very important as other bone substitutes and allograft bone do require removal of the device, if a deep infection occurs and this adds to the complexity and extent of the required operative debridement[48].

Conclusion

The device studied, STIMULAN Rapid Cure mixed with antibiotics, performed as anticipated without any unexpected adverse events and did not inhibit fracture healing. (Figure 4) It delivered local antibiotics, absorbed as expected

and permitted normal bone healing over six months in the majority (80%) of our participants. Ninety-six percent were healed by 12 months. This appears equal to or better than vancomycin powder with the additional options of other antibiotic choices, as required by each individual patient and did not seem to provide predilection to gram negative infections. Our participant population suffered the same complications expected from this fracture population. None of the complications were attributed directly to the study device based on the evaluation of an adjudication committee.

Bone substitutes and allograft do add some support to the subchondral defect but the choice of the plate fixation construct plus the operative reduction of the deformity must be sufficient to support the joint surface over the healing period.

We were able to establish that this device is safe, absorbs as expected, allows osseous replacement, and delivers antibiotics locally (bone and surrounding soft tissue) without harming the patient. There were no increased wound drainage or subchondral cysts as suggested in previous studies evaluating calcium sulfate. This device could be beneficial in high-risk patients with acute fractures and patients with known bone infections. This pilot trial will inform a prospective randomized multicenter study to further evaluate this device in the management of musculoskeletal infections.

Source of Funding:

Funding for this study was provided by an independent research grant from Biocomposites, Ltd. The research proposal and protocol design were conceived by the primary investigator. Biocomposites, Ltd. also provided the STIMULAN Rapid Cure.

Trial Registration:

ClinicalTrials.gov: NCT02456194

Presentation of Results:

Results have been presented at the annual meetings of the Orthopaedic Trauma Association (2019), Canadian Orthopaedic Association (2020) and American Orthopaedic Association (2021).

FDA Status:

Mixing antibiotics with STIMULAN Rapid Cure is off-label in the USA.

Conflict of Interest Statement:

All authors received grant funding and STIMULAN Rapid Cure from Biocomposites, Ltd. to conduct the study. Dr. Leighton reports speaker fees from Zimmer and Bioventis and grants from Johnson & Johnson and Smith & Nephew outside the submitted work. The remaining authors have indicated they have no other financial relationships relevant to this article to disclose.

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Participating sites: Nova Scotia Health, Halifax, NS, Canada: Ross Leighton, Rashed Alqudhaya, Gerald Reardon, Ivan Wong, Michael Biddulph, Shelley MacDonald, Kelly Trask. Foothills Medical Centre, Calgary, AB, Canada: Prism Schneider, Richard Buckley, Paul J. Duffy, Robert Korley, C. Ryan Martin, Tanja Harrison, Leah Kennedy, Aftab Akbari, Stephanie Carli Yee. Hôpital du Sacré-Coeur de Montréal, Montreal, QC, Canada: Jonah Hébert-Davies, Dominique Rouleau, George Yves Laflamme, Julie Fournier, Karine Tardif. Horizon Health Network, Moncton, NB, Canada: Michael E. Forsythe, Sylvia Gautreau. Eastern Regional Health Authority, St. John's, NL, Canada: Andrew Furey, Erin Baker, Sarah Anthony, Tanya Nolan.

References:

1. Segal D, Franchi AV, Campanile J. Iliac autograft for reconstruction of severely depressed fracture of a lateral tibial plateau. Brief note. *The Journal of bone and joint surgery*. 1985; 67:1270-1272.

2. Fowler BL, Dall BE, Rowe DE. Complications associated with harvesting autogenous iliac bone graft. *American journal of orthopedics (Belle Mead, NJ*. 1995;24:895-903.

3. Goulet JA, Senunas LE, DeSilva GL, et al. Autogenous iliac crest bone graft. Complications and functional assessment. *Clinical orthopaedics and related research*. 1997:76-81.

4. Seiler JG, 3rd, Johnson J. Iliac crest autogenous bone grafting: donor site complications. *Journal of the Southern Orthopaedic Association*. 2000;9:91-97.

5. St John TA, Vaccaro AR, Sah AP, et al. Physical and monetary costs associated with autogenous bone graft harvesting. *American journal of orthopedics (Belle Mead, NJ*. 2003;32:18-23.

6. Younger EM, Chapman MW. Morbidity at bone graft donor sites. *Journal of orthopaedic trauma*. 1989;3:192-195.

7. 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. *The Journal of bone and joint surgery*. 2008;90:2057-2061.

8. Trenholm A, Landry S, McLaughlin K, et al. Comparative fixation of tibial plateau fractures using alpha-BSM, a calcium phosphate cement, versus cancellous bone graft. *J Orthop Trauma*. 2005;19:698-702.

9. Adogwa O, Elsamadicy AA, Sergesketter A, et al. Prophylactic use of intraoperative vancomycin powder and postoperative infection: an analysis of microbiological patterns in 1200 consecutive surgical cases. *J Neurosurg Spine*. 2017;27:328-334.

10. Wichelhaus TA, Dingeldein E, Rauschmann M, et al. Elution characteristics of vancomycin, teicoplanin, gentamicin and clindamycin from calcium sulphate beads. *J Antimicrob Chemother*. 2001;48:117-119.

11. Dreesmann H. über Knochenplombierung. *Klinische Chirurgie*. 1892:804-810.

12. Thomas MV, Puleo DA. Calcium sulfate: Properties and clinical applications. *J Biomed Mater Res B Appl Biomater*. 2009;88:597-610.

13. Beuerlein MJ, McKee MD. Calcium sulfates: what is the evidence? *Journal of orthopaedic trauma*.24 Suppl 1:S46-51.

14. Welch RD, Zhang H, Bronson DG. Experimental tibial plateau fractures augmented with calcium phosphate cement or autologous bone graft. *The Journal of bone and joint surgery American volume*. 2003;85:222-231.

15. Moed BR, Willson Carr SE, Craig JG, et al. Calcium sulfate used as bone graft substitute in acetabular fracture fixation. *Clin Orthop Relat Res*. 2003:303-309.

16. Young MJ, Barrack RL. Complications of internal fixation of tibial plateau fractures. *Orthopaedic review*. 1994;23:149-154.

17. Berkson EM, Virkus WW. High-energy tibial plateau fractures. *The Journal of the American Academy of Orthopaedic Surgeons*. 2006;14:20-31.

18. Bachoura A, Guitton TG, Smith RM, et al. Infirmity and injury complexity are risk factors

for surgical-site infection after operative fracture care. *Clinical orthopaedics and related research*.469:2621-2630.

19. Abdellatif IE. Local application of calcium sulphate impregnated with vancomycin and tobramycin in the treatment of chronic osteomyelitis. *Al-Azhar Assiut Medical Journal*. 2014;12:96-109.

20. Agarwal S, Healey B. The use of antibiotic impregnated absorbable calcium sulphate beads in management of infected joint replacement prostheses. *Journal of Arthroscopy and Joint Surgery*. 2014;1:72-75.

21. Aiken SS, Cooper JJ, Florance H, et al. Local release of antibiotics for surgical site infection management using high-purity calcium sulfate: an in vitro elution study. *Surg Infect (Larchmt)*. 2015;16:54-61.

22. Badie AA, Arafa MS. One-stage surgery for adult chronic osteomyelitis: concomitant use of antibiotic-loaded calcium sulphate and bone marrow aspirate. *International orthopaedics*. 2018.

23. Cooper JJ, Florance H, McKinnon JL, et al. Elution profiles of tobramycin and vancomycin from high-purity calcium sulphate beads incubated in a range of simulated body fluids. *Journal of biomaterials applications*. 2016;31:357-365.

24. Gauland C. Managing lower-extremity osteomyelitis locally with surgical debridement and synthetic calcium sulfate antibiotic tablets. *Advances in skin & wound care*.24:515-523.

25. Laycock PA, Cooper JJ, Howlin RP, et al. In Vitro Efficacy of Antibiotics Released from Calcium Sulfate Bone Void Filler Beads. *Materials (Basel, Switzerland)*.11.

26. Luo S, Jiang T, Yang Y, et al. Combination therapy with vancomycin-loaded calcium sulfate and vancomycin-loaded PMMA in the treatment of chronic osteomyelitis. *BMC Musculoskeletal Disorders*. 2016;17:502.

27. Masrouha KZ, Raad ME, Saghieh SS. A novel treatment approach to infected nonunion of long bones without systemic antibiotics. *Strategies in trauma and limb reconstruction (Online)*. 2018.

28. McPherson EJ, Dipane MV, Sherif SM. Dissolvable Antibiotic Beads in Treatment of Periprosthetic Joint Infection and Revision Arthroplasty. The Use of Synthetic Pure Calcium Sulfate (Stimulan®)Impregnated with Vancomycin & Tobramycin. *Reconstructive Review*. 2013;3:32-43.

29. Papagelopoulos PJ, Mavrogenis AF, Tsiodras S, et al. Calcium sulphate delivery system with tobramycin for the treatment of chronic calcaneal osteomyelitis. *The Journal of international medical research*. 2006;34: 704-712.

30. Parihar M, Ahuja D. Infected Nonunion of Radius and Ulna - Strategy of Approach. *Journal of orthopaedic case reports*.2:26-31.

31. Stancil RD, Summers NW, Fernando ND, et al. Prophylactic Use Of Antibiotic Impregnated Calcium Sulfate Beads In Revision Hip And Knee Arthroplasty Procedures At High Risk For Prosthetic Joint Infection. *Discoveries*. Seattle, WA, USA.: Department of Orthopaedics and Sports Medicine, University of Washington, Seattle, WA 98195; 2016:56-58.

32. Swords K, Martinez DR, Lockhart JL, et al. A Preliminary Report on the Usage of an Intracorporal Antibiotic Cast with Synthetic High Purity CaSO4 for the Treatment of Infected Penile Implant. *The journal of sexual medicine*. 2013;10:1162-1169.

33. Zhou R, Pillai A. A Case Report on the Treatment of Methicillin-Resistant Staphylococcus Aureus (MRSA) Infected Tibial Internal Fixation with Calcium Sulfate. *Orthop Muscular Syst*. 2015;4.

34. Kelly CM, Wilkins RM, Gitelis S, et al. The use of a surgical grade calcium sulfate as a bone graft substitute: results of a multicenter trial. *Clinical orthopaedics and related research*. 2001:42-50.

35. Yu B, Han K, Ma H, et al. Treatment of tibial plateau fractures with high strength injectable calcium sulphate. *International orthopaedics*. 2009;33:1127-1133.

36. Roos EM, Lohmander LS. The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. *Health and quality of life outcomes*. 2003;1:64.

37. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *Journal of biomedical informatics*. 2009;42:377-381.

38. Borade A, Kempegowda H, Richard R, et al. Is "Early Total Care" a Safe and Effective Alternative to "Staged Protocol" for the Treatment of Schatzker IV-VI Tibial Plateau Fractures in Patients Older Than 50 Years? *Journal of orthopaedic trauma*.31:e400-e406.

39. Bove F, Sala F, Capitani P, et al. Treatment of fractures of the tibial plateau (Schatzker VI) with external fixators versus plate osteosynthesis. *Injury*.49 Suppl 3:S12-S18.

40. Bajammal SS, Zlowodzki M, Lelwica A, et al. The use of calcium phosphate bone cement in fracture treatment. A meta-analysis of randomized trials. *J Bone Joint Surg Am*. 2008;90:1186-1196.

41. Ghobrial GM, Thakkar V, Andrews E, et al. Intraoperative vancomycin use in spinal surgery: single institution experience and microbial trends. *Spine*. 2014;39.

42. Bakhsheshian J, Dahdaleh NS, Lam SK, et al. The use of vancomycin powder in modern spine surgery: systematic review and meta-analysis of the clinical evidence. *World neurosurgery*. 2015;83.

43. Ghobrial GM, Cadotte DW, Williams K, et al. Complications from the use of intrawound vancomycin in lumbar spinal surgery: a systematic review. *Neurosurgical focus*. 2015;39.

44. DG K, TF H, SC W, et al. Intrasite vancomycin powder for the prevention of surgical site infection in spine surgery: a systematic literature review. *The spine journal : official journal of the North American Spine Society*. 2015;15.

45. Tubaki VR, Rajasekaran S, Shetty AP. Effects of using intravenous antibiotic only versus local intrawound vancomycin antibiotic powder application in addition to intravenous antibiotics on postoperative infection in spine surgery in 907 patients. *Spine*. 2013;38.

46. Johnson JD, Nessler JM, Horazdovsky RD, et al. Serum and Wound Vancomycin Levels After Intrawound Administration in Primary Total Joint Arthroplasty. *The Journal of arthroplasty*. 2017;32.

47. Bai B, Kummer FJ, Sala DA, et al. Effect of articular step-off and meniscectomy on joint alignment and contact pressures for fractures of the lateral tibial plateau. *Journal of orthopaedic trauma*. 2001;15:101-106.

48. Buckley RE, Seadon S. Infections in calcaneal fracture patients treated with open reduction and internal fixation and bioresorbable calcium phosphate paste: a case series. *Foot & ankle international*.33:997-1000.