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Original article

Role of STIMULAN in chronic osteomyelitis-A randomised blinded study on 95 patients comparing 3 antibiotic compositions, bead quality, forming & absorption time

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ABSTRACT

Introduction: Chronic Osteomyelitis is a well-known clinical entity affecting patients holistically and presents with multiple treatment challenges. Local antibiotic delivery with biodegradable drug carriers has shown promising results.

Materials and methods: Prospective multicenter study performed at 2 centers from November 2021 to January 2023 on 95 osteomyelitis patients treated with surgical debridement & STIMULAN™ for local antibiotic delivery. Patients were randomized into 3 groups. Authors compared antibiotic combinations, bead quality, bead setting, and resorption time for calcium sulfate beads- STIMULAN™. Additionally, organisms isolated, WBC Turnover time, Hypersensitivity Reactions, Recurrence, and Revision Rates were documented.

Results: 95 patients underwent surgical debridement and STIMULAN™ bead application for chronic osteomyelitis. The proximal 1/3rd tibia was commonly affected. The most common symptoms were sinus and pus discharge in 96.84 % & 86.31 % of patients respectively ($p < 0.001$). *Staphylococcus aureus* & MRSA were isolated in 37.8 % & 29.4 % of the patient's wound culture respectively. Bead setting time in Descending order was Group 3 > Group 2 > Group 1 ($p < 0.001$). Bead setting first in Group 1 followed by Group 3 & 2. On compression, Group-1 beads withstood maximum compression forces & had smooth even bead surfaces. On radiographs, 1/3rd bead volume in ascending order was Group 3 > Group 2 > Group 1 ($p < 0.001$). 2/3rd reduction in ascending order was Group 3 > Group 2 > Group 1. Complete bead absorption was earliest seen in Group 3 followed by Group 2 & Group 1 ($p < 0.001$). Recurrence in 2 patients (Group 2) at 6 weeks. Revision rate: 2.10 %. There were no incidences of hypersensitivity. Suture removal was done at 16 ± 2 days.

Conclusion: STIMULAN™ combination with tobramycin, vancomycin, and gentamycin is stable, and forms uniform beads with predictable drug elution & bead resorption with negligible side effects. A mixture with higher liquid content sets later, forms softer beads, and resorbs earlier.

1. Introduction

Chronic osteomyelitis is a persistently challenging condition due to intricate etiology,[1] diagnostic challenges[2] and limited treatment options that detrimentally impacts the quality of life of affected patients and poses significant treatment complexities for clinicians. It is defined as a continuous infection of the bone and often necessitates an integrated management approach that typically involves surgical debridement and extended antibiotic therapy. The primary hurdles in managing chronic osteomyelitis are the multidrug resistance of common pathogens, the suboptimal penetration of antibiotics into infected osseous tissues, and patient compliance issues. Traditional management strategies have predominantly focused on the excision of necrotic bone and the administration of systemic antibiotics. Nevertheless, these conventional

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methods frequently encounter limitations due to the aforementioned challenges, underscoring the urgent need for innovative therapeutic modalities.

The emergence of biofilm-forming bacteria that are resistant to standard treatments necessitates the development of novel treatment approaches for chronic osteomyelitis. The introduction of antibiotic-loaded calcium sulfate beads offers a promising solution by enabling the direct delivery of high local concentrations of antibiotics to the infection site, thus improving therapeutic outcomes while reducing systemic side effects. However, recent studies, including systematic reviews and hierarchical synchrotron diffraction and imaging analyses, have indicated both the potential benefits and the challenges associated with the use of calcium sulfate beads, such as issues related to wound leakage and the material's stability under physiological conditions.[3–5] These findings highlight the critical importance of optimizing bead composition and delivery techniques to maximize therapeutic efficacy and ensure patient safety.

Despite the promising advancements in local antibiotic delivery systems, such as the use of biodegradable drug carriers like calcium sulfate beads (STIMULAN™), the literature reveals significant gaps in standardized protocols, comprehensive outcome data, and detailed analyses of bead quality and kinetics. These gaps persist in the context of chronic osteomyelitis treatment, where multidrug resistance, poor drug penetration, and patient compliance further complicate effective management. Currently, there is no universally accepted protocol for treating chronic osteomyelitis, and treatment strategies vary depending on the surgeon's expertise and the patient's financial situation.[6,7]

In response to these challenges, this study aims to systematically compare the effectiveness of different antibiotic combinations delivered via STIMULAN™ beads in patients with chronic osteomyelitis. This multicenter, randomized, blinded trial is designed to evaluate bead quality, formation, and absorption times, in addition to documenting patient-specific parameters such as organisms isolated, wound discharge characteristics, and hypersensitivity reactions. The study aimed to evaluate the quality, setting times, and resorption rates of STIMULAN™ beads loaded with various antibiotic compositions and additionally to assess the clinical outcomes and patient-specific parameters in the management of chronic osteomyelitis using STIMULAN™ beads as a local antibiotic delivery system. By addressing these objectives, our research aims to significantly contribute to the development of evidence-based protocols for the use of local antibiotic delivery systems in treating chronic osteomyelitis, thereby enhancing patient care and clinical outcomes. This initiative marks a critical step towards filling the existing knowledge gaps and optimizing treatment strategies for this complex condition.

2. Material and methods

Study Design and Setting: A prospective multicenter study was conducted at two centers, patients enrolled between November 2021 to January 2023. The patients enrolled during this time, constituted the study group. The study included patients diagnosed with osteomyelitis, who were treated with surgical debridement followed by the application of STIMULAN™ for local antibiotic delivery. Patients were randomized into three distinct groups, with the randomization process utilizing a computer-generated number system.

Outcomes Assessment: The primary outcomes of this study were to assess the initial bead setting time, bead formation time, quality, bead's absorption time (radiograph assessment). The secondary outcomes were to document the surgical scar condition, wound discharge, hypersensitivity reactions, WBC turnover time, time to suture removal, recurrence incidence, and revision rates.

Inclusion Criteria: Participants included were males and females aged between 12 and 92 years, presenting with discharge (pus or bone) and osteomyelitis in long bones (femur, tibia, humerus). Eligibility required an injury and/or surgery history, culture sensitivity to at least two out of three antibiotics (gentamycin, tobramycin, and vancomycin), Magnetic Resonance Imaging (MRI) confirmed osteomyelitis, and availability for 1-year follow-up.

Exclusion Criteria: Exclusion criteria encompassed refusal to consent, loss to follow-up, resistance to any two of the antibiotics (gentamycin, tobramycin, or vancomycin) as per culture results, and polymicrobial infection.

Surgical Technique: The surgical procedure involved placing patients on a radiolucent table and administering ultrasound-guided regional blocks tailored to the bone involved. Surgical areas were painted and draped in the standard manner. Aseptic precautions were followed during soft tissue dissection and subsequent cauterization and curettage of the medullary canal (see Fig. 1). No tourniquets or Romovac drains were used. The preparation and application of the STIMULAN™ and antibiotic mixture followed a precise protocol detailed below.

STIMULAN™ Preparation Protocol: A standardized procedure was employed for preparing the STIMULAN™ mixture. Under standards operating conditions (operating room temperature: 180 Celsius and humidity: 55 %), the STIMULAN powder (5 cc) was put in mixing chamber, vancomycin & gentamycin powder was mixed using spatula evenly. Tobramycin Liquid was added, and mixing was continued. Lastly, STIMULAN liquid was added to the mixture till no power was left & a smooth paste was made, gently transferred to the bead mat for bead setting. Authors made large beads (6 mm) and medium beads (4.8 mm) were made only when extra material was available. Bead formation was confirmed by bending the STIMULAN mat to see id bead mat edges and beads separated well; confirming bead setting (see Fig. 2). Authors retrieved 12 cc beads from 5 cc STIMULAN in the bead retrieval chamber, to be implanted later.

Antibiotic Mix Protocol: Group-1: Vancomycin powder- (500 mg x 2) + Gentamycin liquid- (80mg/2 ml x 2). Group-2: Vancomycin powder- (500 mg x 2) + Gentamycin liquid- (80mg/2 ml x 1) + Tobramycin liquid- (80mg/2 ml x 1). Group-3: Vancomycin (500 mg x 3) + Gentamycin liquid- (80mg/2 ml x 1) + Tobramycin liquid- (80mg/2 ml x 2).

Randomization and Blinding Protocol: Patients were blindly randomized into three groups, differing only in the antibiotic mix used. The surgical team and the doctors responsible for follow-up assessments were kept blind to patient groupings.

Radiograph Assessment: 3 clinicians reviewed digital radiographs postoperatively for bead appearance and absorption assessment. Bone cavity assessed with Anteroposterior view for medial/lateral assessment & Lateral view for anterior/posterior assessment (see Fig. 3). CT scans were performed to confirm resorption/integration in selected cases.

Antibiotic Protocol: Intravenous Antibiotics (Cefuroxime 1.5 gm BD, Gentamycin 500 mg BD and Metronidazole 500 mg TDS) for 3 days followed by Oral Antibiotics in combination (Cefuroxime 500 mg BD, Linezolid 600 mb BD, Metronidazole 400 mg TDS and Vancomycin 250 mg) for 4–6 weeks customized depending on Organism Isolated and Wound behaviour.

Rehabilitation & Follow-up Protocol: Slab support for 2 weeks. Bed rest from 4 to 5 days. Joint movements encouraged 6–8 h after surgery. For lower limb affection, non-weight bearing assisted walking allowed same day, toe walking allowed at 1 week. Unassisted walking started at 3 weeks. The follow-up schedule included in-person visits for dressing changes, suture removal, and regular assessments up to one-year post-surgery.

Statistical Analysis: SPSS version 26.0, IBM Corp, Chicago, Illinois, USA was used for data analysis. The statistical approach involved paired sample t-tests for pre and postoperative outcomes comparison, with independent two-sample t-tests and Chi-Square tests comparing clinical results between groups. A significance level of P-value <0.001 was established.

3. Results

95 patients included in the study group underwent surgical

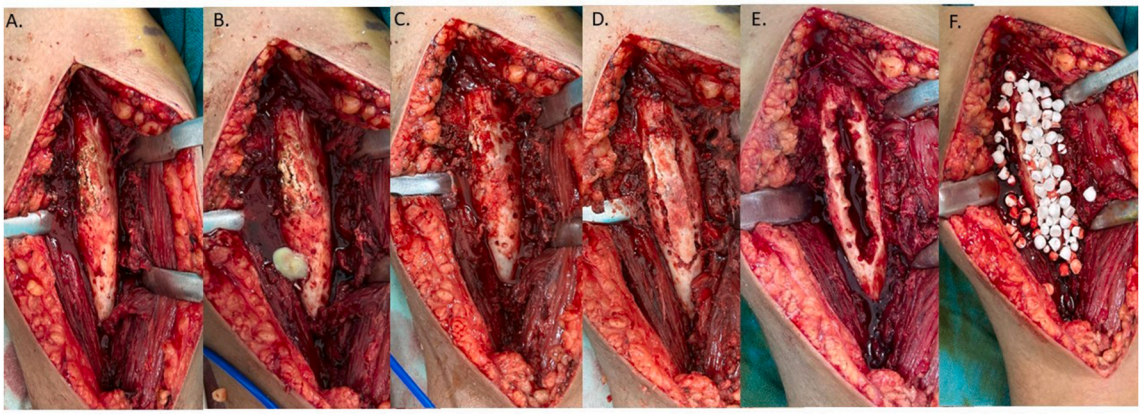

Fig. 1. Debridement & Antibiotic Bead Surgery (Steps): A: Identification of Affected Swollen Area in Humerus Shaft, B: Bone Tap revealed Intraosseous Pus, C: Multiple Drill Holes to Outline Bony Window, D: Connecting Drill Holes to Facilitate Bony Roof Removal, E: Removal of Bony Roof (Saucerization), F: Antibiotic Beads Application (inside bone & in surrounding tissue).

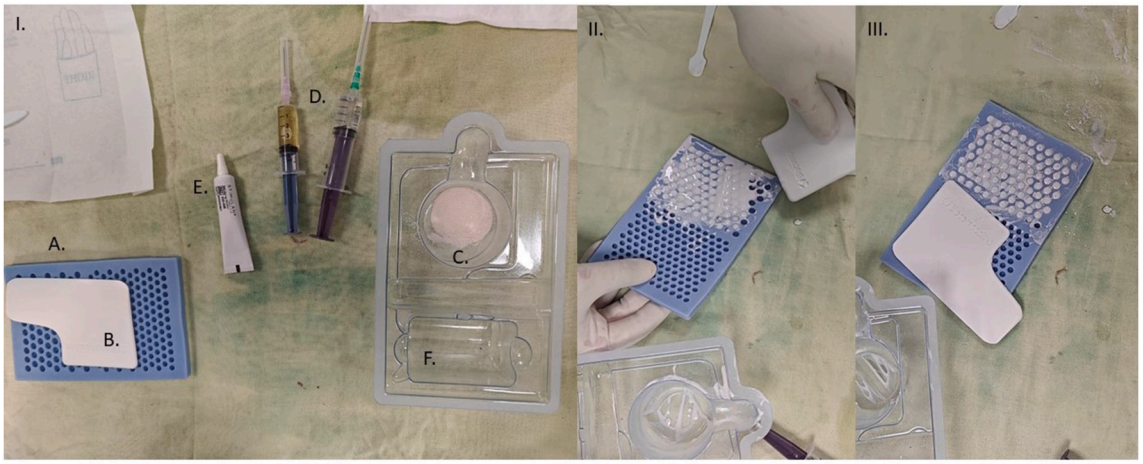

Fig. 2. Stimulan^{tm} Preparation (steps): I- Stimulan^{tm} Rapid Cure Kit Components: A- Bead Mat, B- Spatula, C- Mixing Chamber (Powder + Antibiotic), D- Antibiotics, E− Stimulan^{tm} Liquid, F- Bead Retrieval Chamber. II- Introducing Stimulan^{tm} + Antibiotic Mix into Bead Mat for Setting. III- Resting time to allow for Bead setting.

debridement and STIMULAN™ bead application for chronic osteomyelitis. Group-1 & 2 had 32 patients and Group-3 had 31 patients. The mean age of patients was 27.12 years (S.D - 5.75). The maximum patients (34.51 %) belong to groups 20–35 years. Male: Female ratio was 1.6:1 with 59 males (62.11 %) and 36 females (37.89 %) being a part of the study group. The most affected site was the proximal 1/3rd tibia in 30.52 % of patients.

Non-healing wound or sinus was the most common presenting symptom in 92/95 (96.84 %) patients followed by pus discharge in 82/95 (86.31 %) patients ($p < 0.001$). 78 patients (82.10 %, $p < 0.001$) were operated on before and had retained hardware at the time of enrollment. The demographic and preoperative characteristics of the patients were statistically similar (Table 1). The most common organism isolated was *Staphylococcus aureus* in 37.8 % (36/95) patients followed by Methicillin-Resistant *Staphylococcus aureus* (MRSA) in 29.4 % (28/95) patients & Coagulase Negative *Staphylococcus aureus* in 10.52 % (10/95) patients. Organisms isolated from wound culture group-wise are listed in Table 2.

Regarding the primary outcomes assessment for STIMULAN™ (5 cc), the complete bead setting time was Group 3 (18.20 min) > Group 2 (17.40 min) > Group 1 (16.25 min) ($p < 0.001$). Beads were seen setting first in Group 1 (12.20 min) followed by Group 3 (12.40 min) and Group 2 (13.15 min). The beads formed in all 3 groups, and the intact beads were weighed, the highest yield was obtained in Group 3 (13.4 g) followed by Group 1 (13.1 g) and Group 2 (12.9 g). On compression, Group 1 beads withstood maximum compression forces before breaking. Group 1 beads had better quality in terms of surface smoothness & evenness. The STIMULAN™ bead variables are listed in Table 3.

The radiographic assessment was performed by 3 researchers, mean of 3 readings weas obtained for all groups. A 100 % bead volume was observed on the immediate post-operative radiograph. 1/3rd reduction was earliest in Group 3 (22 days), followed by Group 2 (24 days) & Group 1 (28 days) ($p < 0.001$). 2/3rd reduction in ascending order was Group 3 (39 days) > Group 2 (41 days) > Group 1 (42 days). Complete bead absorption was seen first in Group 3 (66 days) followed by Group 2 (72 days) & Group 1 (76 days) ($p < 0.001$). The radiograph assessment variables are listed in Table 4.

Regarding Secondary outcome assessment, remission in pus discharge was seen in 93 patients. 2 patients with pus recurrence at the 6-week review were seen in Group 2, they were on steroids for rheumatoid arthritis. They were re-operated later; thus, the revision rate was 2.10 %. Surgical wounds healed in all patients. There were no incidences of hypersensitivity. Suture removal was done at 16 ± 2 days. Authors observed a WBC turnover in 65/95 (68 %) patients on POD-5 & in 93/95 (98 %) at 2 weeks. 93 out of 95 patients (97.89 %) were satisfied with the primary surgical procedure. At 1 year follow-up, 100 % of patients were symptom-free.

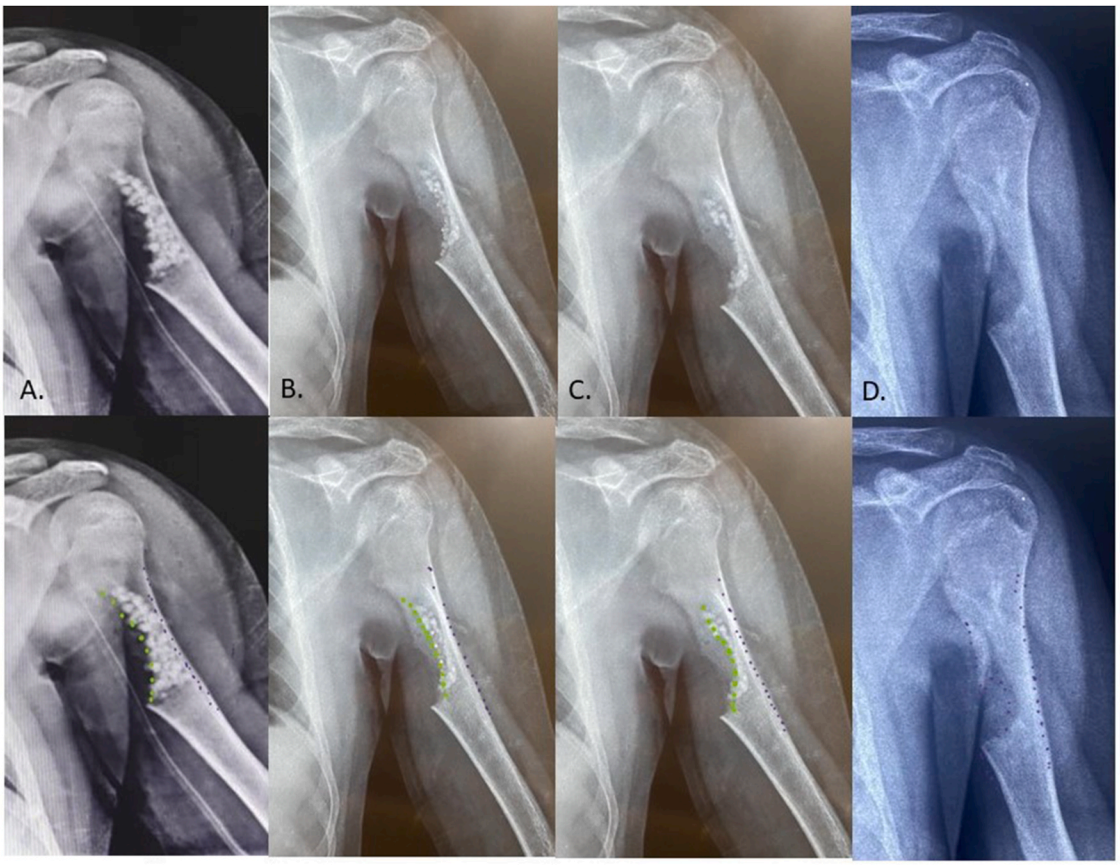

Fig. 3. Stimulan™ Bead Volume Assessment (Lateral View): A- 100 % Bead Volume, B- 66 % Bead Volume or 1/3rd Reduction, C- 33 % Bead Volume or 2/3rd Reduction, D- No Beads visible (100 % Absorption). (Green-Stimulan Margin, Purple- Reference Cortex).

4. Discussion

Even today, Osteomyelitis is a common but serious health-disabling ailment directly affecting a person's Quality of life[8] and Social Status. Major concerns while treating chronic osteomyelitis are infected tissue clearance (debridement), local drug delivery, and dead space management. It is reported that patients with residual dead space are highly prone to infection or re-infections.[9] In infected scenarios, local devascularization of tissue prevents penetration of antibiotics into affected tissue; additionally, residual biofilms[10] can shield the area from antibiotics. Biodegradable systems that can fill voids and support local antibiotic release in the presence of infection offer solutions to these problems.

Biodegradable bone void fillers are either calcium sulfate or calcium phosphate-based. Calcium sulfate-based derivatives mimic closely to human body composition owing to their biocompatibility, porosity, and biodegradability.[11] In addition, they function as osteoconductive bio-scaffolds for osteogenic cells & blood vessels[12,13] and stimulate new bone formation at a rate comparable with autogenous bone.[14,15] This material can exist as tricalcium phosphate or hydroxyapatite.[16] Calcium Phosphate's Hydroxyapatite (HA) form is the most abundant form in the human body, accounting for 70–75 % of the bone's mineral content by weight.

STIMULAN™ is a porous calcium sulfate-based biodegradable carrier meant for use as a dead space filler and local antibiotic delivery; with evidence-backed literature to prove its worth. Easily mixable with liquid and powder antibiotics like Gentamycin, Tobramycin, and Vancomycin which in combination cover most organisms causing osteomyelitis in children and adults. Predictable, supra-therapeutic elution profile.[8] STIMULAN™ has a supra-therapeutic elution profile[17] of 40–42 days with proven action against biofilms, especially *Staphylococcus aureus* and *Pseudomonas aeroginosa*.[18] Additionally, it does not act as a nidus for infection[18] or cause third-body damage.

Once placed inside the bone, calcium sulfate beads incorporate completely into the parent bone matrix[19] and resorb completely at an optimal rate, leaving behind no Hydroxyapatite or insoluble impurities. Scanty serous discharge from the implanted site has been reported by some authors, but we did not come across such complications or adverse skin reactions at the implanted site till complete follow-up of all patients. The advent of calcium sulfate biodegradable carriers serving multiple roles has surely improved the successful results of the treatment of chronic osteomyelitis.

Authors report the initial bead setting time range from 12.20 to 13.15 min. The fastest was seen in Group 1 with more powder ingredients (STIMULAN™ powder & vancomycin powder) and the slowest in Group 3 with high liquid content (stimulant™ liquid, tobramycin, and gentamycin liquid). But complete beads formed in all 3 groups. The beads of Group 1 were harder, and most beads were complete & smooth. Group 3 beads had imperfections & were softer as compared to Group 1 but were of acceptable quality post-formation. The final bead setting time range was 16.25–18.20 min. Beads formed completely first in Group 1 as I had relatively less liquid material. Group-3 (18.20 min) beads were last to form but had the highest yield in terms of dry weight (13.4 g). This could be due to relatively increased powder & liquid material added to the pre-mix compared to other groups.

Beads of Group-3 contained a fixed 3-antibiotic combination (vancomycin, tobramycin & gentamycin); this combination can be helpful in patients with polymicrobial sensitive flora. The authors observed satisfactory bead formation with enhanced yield compared to other groups. On, Radiographic assessment Group-3 (3-antibiotic combination) beads had an early (initial & complete) reduction in bead volume, this can be attributed to their soft nature and higher liquid content but still, they

Table 1
Demographic and preoperative patient data.

Characteristic	Group-1 (2V+2G) (n-32)	Group-2 (2V+2G + T) (n-32)	Group-3 (3V + G+2T) (n-31)	*p*-value
Age (yr)	28.10 ± 4.24	26.32 ± 5.16	29.40 ± 4.81	0.34
Sex (male: female)	21 (53.3): 11 (46.6)	19 (52.4): 13 (47.6)	19 (61.2): 12 (38.8)	0.06
Symptom duration (weeks)	25.36 ± 5.23	26.84 ± 3.94	28.14 ± 2.28	0.21
Bone Involved				0.65
Humerus (upper 1/3)	4 (12.5)	5 (15.6)	4 (12.9)	
Humerus (middle 1/3)	2 (6.2)	2 (6.2)	1 (3.2)	
Humerus (lower 1/3)	–	–	1 (3.2)	
Femur (upper 1/3)	2 (6.2)	2 (6.2)	3 (9.6)	
Femur (middle 1/3)	3 (9.3)	2 (6.2)	2 (6.4)	
Femur (lower 1/3)	–	1 (3.1)	–	
Tibia (upper 1/3)	11 (34.4)	8 (25.0)	10 (32.2)	
Tibia (middle 1/3)	4 (12.5)	5 (15.6)	5 (16.1)	
Tibia lower 1/3)	6 (18.8)	7 (21.8)	5 (16.1)	
Symptom (%)				
Pain	4 (12.5)	5 (15.6)	4 (12.9)	0.65
Pus Discharge	26 (81.2)	27 (84.3)	29 (93.5)	<0.001
Bone Discharge	8 (25.1)	12 (37.5)	8 (25.8)	0.36
Non-Healing Wound/Sinus	30 (93.7)	31 (96.8)	31 (100)	0.11
Previously Operated (Hardware):	24 (75.0)	28 (87.5))	26 (83.8)	<0.001
Previously Operated (No Hardware):	6 (18.7)	4 (12.5)	5 (16.1)	0.45
Co-Morbidities:				
Diabetes	8 (25.0)	6 (18.7)	6 (19.3)	
Immune Compromised (HIV-HbsAg)	6 (18.7)	7 (21.8)	4 (12.9)	
Immune Suppression (Steroids)	3 (9.3)	2 (6.2)	6 (19.3)	
Rheumatoid/ Inflammatory Arthritis	4 (12.5)	2 (6.2)	2 (6.4)	
Hypertension	4 (12.5)	–	3 (9.6)	

Values are presented as mean ± standard deviation or number (%).2V- 1000 mg Vancomycin, 3V- 1500 mg Vancomycin, G- 80 mg Gentamycin, 2G- 160 mg Gentamycin, T- 80 mg Tobramycin, 2T- 160 mg Tobramycin.

Table 2
Organisms isolated from wound culture[a].

Organisms Isolated[b]	Group-1 (2V+2G) (n-32)	Group-2 (2V+2G + T) (n-32)	Group-3 (3V + G+2T) (n-31)
Staphylococcus Aureus	14(43.7)	12(37.5)	10(32.2)
Staphylococcus Aureus (Coagulase [c])	3(9.3)	4(12.5)	3(9.6)
Staphylococcus Aureus (MRSA)[d]	9(28.1)	10(31.2)	9(29.0)
Staphylococcus Epidermidis	1(3.1)	3(9.3)	5(16.1)
Pseudomonas Aeruginosa	3(9.3)	2(6.2)	3(9.6)
Klebsiella Pneumoniae	2(6.2)	1(3.1)	1(3.2)

[a] Wound culture was taken at time of enrolment after washing wound with gentle stream of normal saline.
[b] Vancomycin Culture- 'Vancomycin E-strip'. Tobramycin & Gentamycin Culture- 'Bauer-Kirby Method'.
[c] Values Expressed as Incidence (%).
[d] MRSA- Methicillin Resistant Staphylococcus Aureus.

lasted 66 days (mean) at the implantation site & patients did well in Group 3 clinically and radiologically.

Calcium sulfate biodegradable beads outweigh PMMA cement in some aspects. Firstly, the beads have a rough outer surface, they do not support the organism's growth. Secondly, being a biodegradable

Table 3
STIMULAN variables assessment -clinical.

Variables	Group-1 (2V+2G) (n-32)	Group-2 (2V+2G + T) (n-32)	Group-3 (3V + G+2T) (n-31)	P value
STIMULAN Quantity (cc)	5	5	5	
Antibiotic Quantity-Powder (mg)	1000	1000	1500	
Antibiotic Quantity-Liquid (mg/ml)	160/4	240/6	240/6	
Mixing Time (mins)	1.76	1.28	1.24	0.45
Bead Setting Time-initial (mins)[a]	12.20 (0.30)	13.15 (0.44)	12.40 (0.20)	0.32
Bead setting Time-complete (mins)	16.25 (0.40)	17.40 (1.20)	18.20 (1.10)	<0.001
Bead Quality – Even Surface[b]	+++	+++	++	
Bead Quality-Compression[c]	++++	++	++	
Bead Formation (%)	100	100	100	
Dry Weight-Intact Beads (gm)-approx.	13.1	12.9	13.4	0.24

[a] Values expressed as Mean (S.D).
[b] Visual assessment of bead structure: Shape completeness, evenness of surface, Break in Structure.
[c] Digital Compression of beads: Beads compressed till fingertips blanch, comparative force with which beads collapse was noted.

Table 4
STIMULAN volume assessment – radiographs.

Variables	Group-1 (2V+2G) (n-32)	Group-2 (2V+2G + T) (n-32)	Group-3 (3V + G+2T) (n-31)	p-value
100 % Bead Volume	PoD1[b]	PoD1	PoD1	
66 % Bead Volume (Reduction 1/3rd) [a]	28 (2)/24-31	24 (2)/21-26	22 (2)/19-24	<0.001
33 % Bead Volume (Reduction 2/3rd)	42 (3)/41-46	41 (3)/38-44	39 (2)/37-41	0.34
No Bead Visible (100 % Absorption)	76 (3)/72-81	72 (2)/69-75	66 (3)/62-69	<0.001

- Values expressed in Days (S.D)/Range.
[a] Bead Volume (%) is approximate assessment, assessed on one view on digital radiographs by experienced clinicians. Assessment had high inter-observer variations. Presented values (mean & S.D) is average reading (mean) from 3 observers.
[b] Post operative day 1.

product, it generates biofriendly debris & doesn't require additional procedures for removal.[8,20] One of the concerns with STIMULAN™ can be the cost factor. Presently, 5 cc & 10 cc pack in India costs between 200 and 220 USD & 280–300 USD respectively depending on availability. This should be brought down, or comparable alternatives can be used to cater to a larger patient pool and change the lives of patients suffering from the common but often mistreated 'Chronic Osteomyelitis'.

The strengths of the study are a large study group and assessment of 3 antibiotic combinations with STIMULAN™. Authors define the antibiotic amount to be mixed with Calcium Sulfate; a mix that will surely form antibiotic beads will help clinicians counter microbial flora aggressively with broader coverage and improved efficiency. Authors have radiologically assessed the antibiotic beads elution/incorporation timeline, these data will help standardize the treatment of chronic osteomyelitis. The authors followed up with 95 patients for 12 months, a time sufficient to analyze potential complications and clinical outcomes; the data is important considering limited data on biodegradable antibiotic carriers from the sub-continent.

Limitations of the study: The authors assessed local drug availability indirectly through the presence of antibiotic beads & clinical response. A study assessing local antibiotic availability directly through pharmacological tests can add more information to the author's claim. Secondly, bead hardness was tested by a coarser digital compression test, but exact hardness and ability to resist deformation can be assessed through in-vitro mechanical testing to add more information for this variable. Microscopic analysis of formed beads can be done to document microscopic structure and explore interacting bonds between the monomer, polymer & antibiotics. The authors plan to compare various antibiotic carriers with a larger study group to explore this domain & contribute critical information to published literature.

5. Conclusions

STIMULAN™ is a promising surgeon's tool for use in the presence of infection. Solution for local drug delivery and filling voids while treating chronic osteomyelitis. Its combination with tobramycin, vancomycin, and gentamycin is stable and forms uniform beads with predictable drug elution & bead resorption with negligible side effects. Uniform mixing of ingredients and standard operating room conditions facilitate uniform bead formation. A mixture with higher liquid content sets later forms softer beads and resorbs earlier in vivo after being placed in the surgical field.

Conflict of interest

The authors have no financial or other conflict of interest to declare and no financial or other relationships leading to conflict of interest.

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Institution of work

The work was done at Manas Hospital and Rudra Fracture Hospital, NCR, India. Ethical committee clearance was obtained before enrolling patients for the study [MH-2021/10–14] & [RFH-6.2021-05}. Written informed consents were obtained from all participants before the start of study.

Ethical clearance

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CRediT authorship contribution statement

Nishit Palo: Conceptualization, Methodology, Investigation. **Binayak Ray:** Software, Investigation. **Mahima Lakhanpal:** Supervision, Literature Search, Writing – original draft. **Madhan Jeyaraman:** Writing – review & editing, Validation. **Govind Narayan Choudhary:** Investigation, Figure and Table Preparation. **Aditya Singh:** Data curation, Figure and Table Preparation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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