CERAMENT® G
with Gentamicin

PUBLICATION SUMMARY

Medical Education Series

Radiographic and Histological Analysis

CASE SERIES OF 163 PATIENTS

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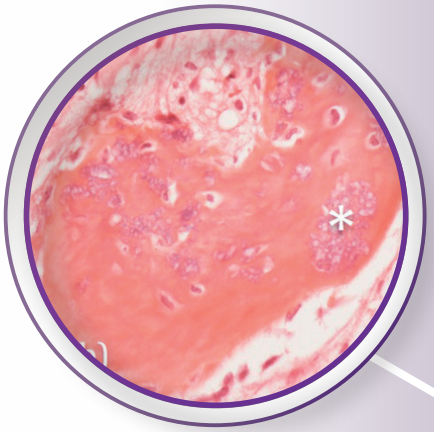


BONESUPPORT™

Radiographic and Histological Analysis

INTRODUCTION

The following is a summary of a study on CERAMENT® G: Radiographic and Histological Analysis of a Synthetic Bone Graft Substitute Eluting Gentamicin in the Treatment of Chronic Osteomyelitis, as published in *Journal of Bone and Joint Infection* 2019; 4(2): 76-84.

METHODS

A retrospective review of a prospectively collected series of 163 patients with Cierny-Mader Type III or IV chronic osteomyelitis who underwent single-stage excision, insertion of CERAMENT® G, and definitive soft tissue closure or coverage and systemic antibiotic therapy.

OUTCOME MEASURES

The primary outcome measure was the percentage of bone void healing at one year post surgery. The secondary outcome measures were infection recurrence rate, subsequent fracture and review of histology data from nine patients who had subsequent surgery unrelated to infection recurrence.

Inclusion Criteria:

- Cierny-Mader (C-M) Type III (localized) and Type IV (diffuse)
- Having chronic osteomyelitis symptoms for at least 6 months accompanied by the presence of a sinus, an abscess or intra-operative pus, supportive histology, or two or more microbiological cultures with indistinguishable organisms.

Exclusion Criteria:

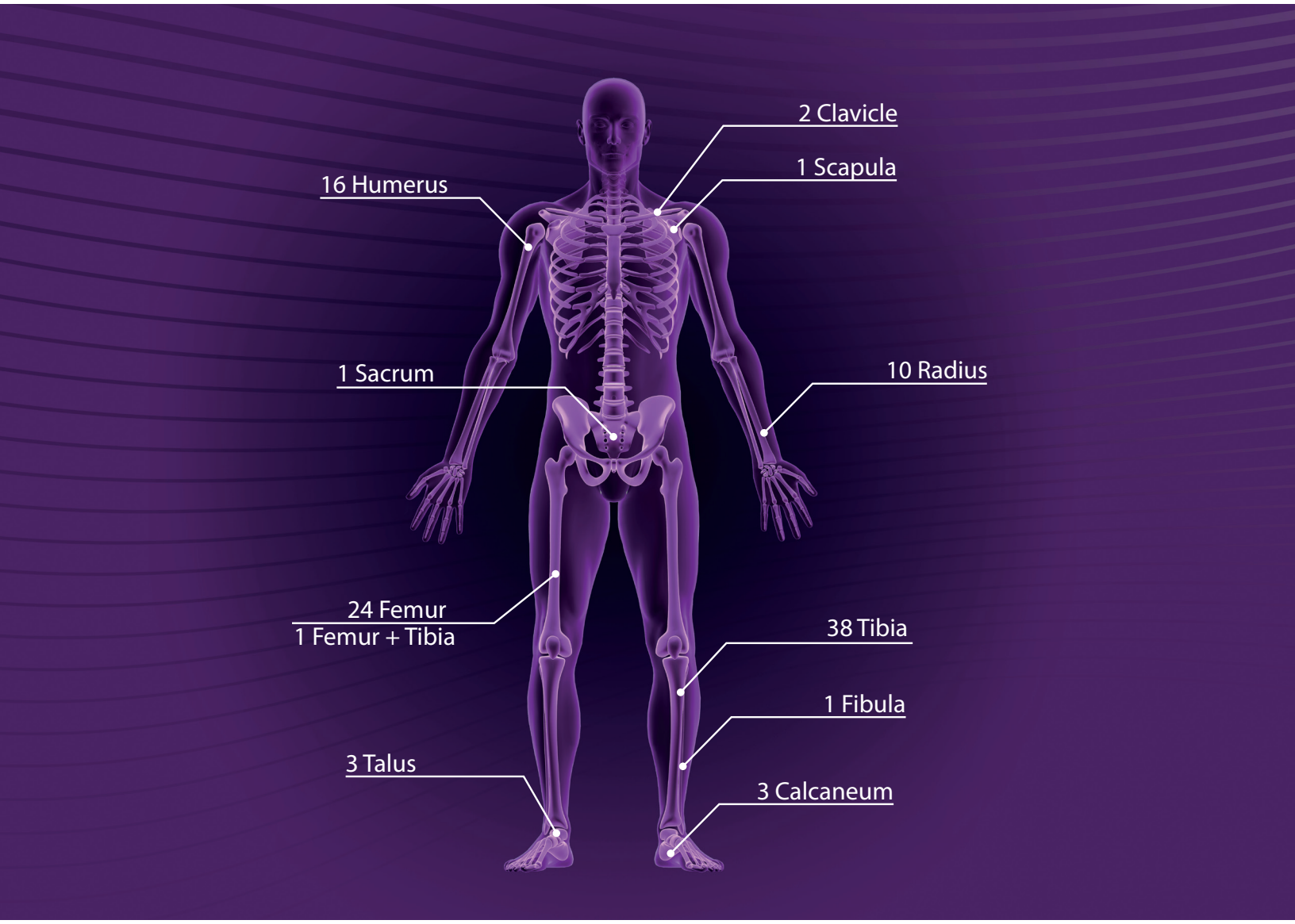
- Patients with osteomyelitis secondary to diabetic foot infection
- Patients with Cierny-Mader Type IV with large segment defects >1cm
- Contraindications according to the IFU

Patient Demographics:

- 163 patients
- 109 males / 54 females
- Mean age 51.6 years (17.8 to 86.1)

Ferguson et al. "Radiographic and Histological Analysis of a Synthetic Bone Graft Substitute Eluting Gentamicin in the Treatment of Chronic Osteomyelitis." Journal of bone and joint infection vol. 4,2 76-84. 16 Mar. 2019

DISTRIBUTION OF CIERNY-MADER ANATOMIC TYPE AND PHYSIOLOGICAL CLASSIFICATION IN THE COHORT OF 154 CASES WITH MINIMUM ONE-YEAR RADIOGRAPHIC FOLLOW-UP



CIERNY-MADER GRADE

	A	B_{local}	$B_{systemic}$	B_{l+s}
III	18	25	19	16
IV	2	4	5	11

MICROBIOLOGY

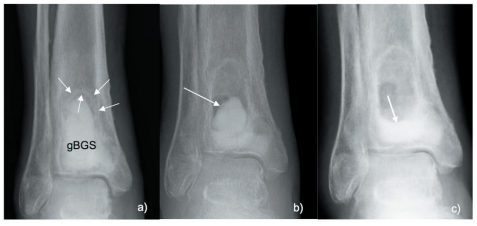
Organism	Total	Fracture related infection	Haemato genous	Infection following elective surgery	Soft tissue injury
Polymicrobial	29	19	2	5	3
No growth	59	37	18	3	1
Monomicrobial	75	46	16	11	2
MSSA	42	22	12	7	1
MRSA	4	3	1		
CoNS	3	3			
Pseudomonas spp.	6	5		1	
Enterobacter cloacae	4	3		1	
Corynebacterium Straitum	3	2		1	
Streptococcus spp.	2	2			
Bacillus spp.	2	1		1	
Serratia Marcescens	2	2			
Achromobacter spp.	2	1			1
Salmonella enteritidis	1		1		
Proteus mirabilis	1	1			
Clostridium Difficile	1	1			
Cutibacterium acnes	1		1		
Mycobacterium tuberculosis	1		1		
	163	102	36	19	6

RADIOGRAPHIC ASSESSMENT

Radiographs of the operated bone were taken immediately post-operatively, at 6 weeks, at 3, 6, and 12 months and yearly thereafter.

There were three distinct radiographic features of CERAMENT® G remodeling which were observed in a minority of cases:

- **"Halo sign"** – A radiopaque hyperdense around the periphery of the bone void and the CERAMENT® G. if present usually appearing on the 6-week follow-up radiographs.
- **"Marble sign"** – Marble-shaped hypodense remnant of the biomaterial noticed up to 3 months after surgery. Later resorption of the CERAMENT® G occurred and the "Marble sign" disappeared.
- **"Puddle sign"** – A hyperdense region of biomaterial accumulating at the bottom of the bone excision site. This finding was usually seen between 3 and 6 months after implementation.

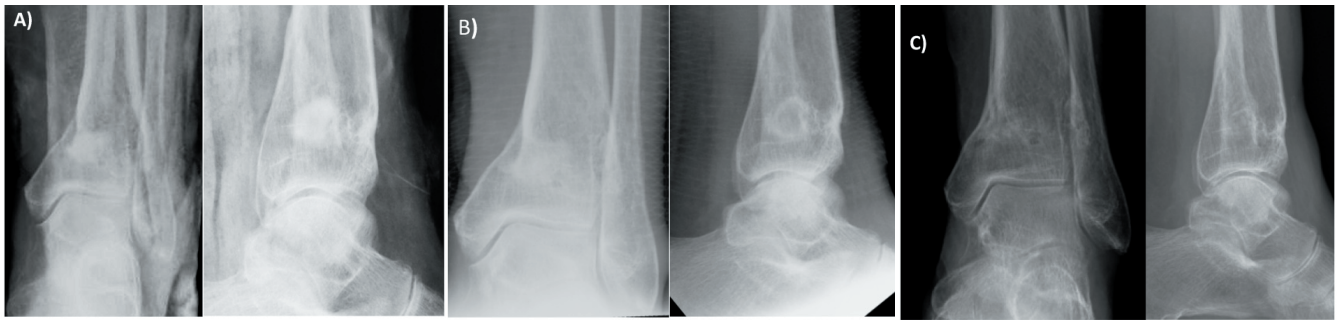


Figures (A) AP radiograph 6 weeks after debridement and filling of an osteomyelitic bone void in the distal tibia. Halo sign: Radio-dense ring around the gBGS (arrows). (B) Marble sign noted at 12 weeks with remnant of the biocomposite appears in the bone void (arrow). (C) Puddle sign at 26 weeks with remnants of the biocomposite accumulating at the bottom of bone void (arrow).

RADIOLOGICAL OUTCOMES

A total of 138 cases had a minimum of 1-year radiographic follow-up. The mean was 1.7 years with a range of 1-4.7 years.

The mean bone-void filling at final follow-up was 74.8% (range 0-100%). Bone void filling was significantly higher in metaphyseal lesions (79.0%) compared to diaphyseal lesions (65.6%) (p=0.017).



(A) Immediate post-operative follow-up radiographs (AP and lateral view) after debridement and filling of an osteomyelitic bone defect of the distal tibia. (B) Follow-up radiographs (AP and lateral view) six weeks following surgery. Note "Halo sign" in lateral view at six weeks (C) Images taken 12 months following surgery. There is almost complete filling of the void with new bone.

Complete void filling, with disappearance of the defect at final follow-up was seen in 34 cases (24.6%). Only 18 cases (13.0%) had less than 50% bone void filling at final follow-up.

Cases where there was good initial interdigitation between the carrier and bone on the immediate post-operative radiographs had significantly better bone healing at final follow-up (77.3% filling versus 68.7%). The volume of the defect was not found to significantly affect the degree of bone healing seen at final follow-up.

Bone formation progressed between the first and second years of follow-up in 63.2% of the 38 cases with more than 2 years of follow-up.

During radiographic follow-up 58/138 (42.0%) had at least one feature of CERAMENT G remodeling (Halo, Marble, or Puddle sign), 30/138 (21.7%) had at least two, and 13/138 (9.4%) had all 3. The three features of CERAMENT® G bone remodeling were significantly more likely to be seen in metaphyseal defects compared to diaphyseal.

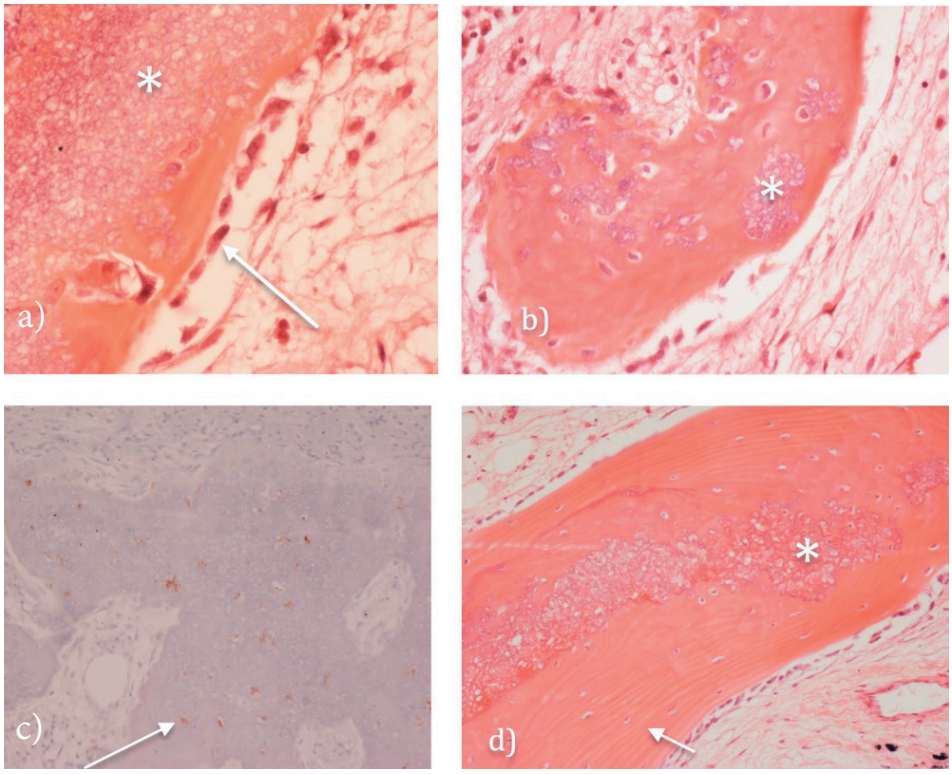
Feature	Metaphysis (n=79)	Diaphysis (n=44)	Combined Metaphysis/ Diaphysis (n=15)
Halo Sign	33 (41.8%) *p=0.023*	10 (22.7%)	4 (26.7%)
Marble Sign	19 (24.1%) *p=0.013*	3 (6.8%)	3 (20.0%)
Puddle Sign	22 (27.8%) *p=0.011*	4 (9.1%)	3 (20.0%)

HISTOLOGICAL RESULTS

There was a total of 9 biopsies studied. In early biopsies (19 days and 2 months), there were focal areas where osteoblastic cells covered CERAMENT® G particles with an osteoid-like matrix.

In biopsies taken 4-5 months following carrier insertion, more evidence of bone formation was observed with trabeculae that contained CERAMENT® G particles. The bone formed was mainly woven but partly lamellar in type. Giant cells on the surface of the newly formed mineralized osteoid and woven bone expressed an osteoclast phenotype.

In later biopsies (up to 2 years), there were increased numbers of larger bone trabeculae within well-vascularized reparative fibrous tissue containing CERAMENT® G particles. Bone trabeculae formed were composed of woven and lamellar bone even though more lamellar bone was seen in biopsies >5 months after CERAMENT® G insertion.



Histology of CERAMENT® G (a) an early biopsy showing CERAMENT® G (see asterisk) covered by an osteoid-like matrix produced by osteoblastic cells seen lining the gBGS surface (see arrow). (b) shows focal mineralisation of the osteoid matrix and early woven bone formation around the residual gBGS (see asterisk). (c) immunohistochemistry demonstrating osteocytes in woven bone (brown staining) around the gBGS, expressing dentine matrix protein-1 (DMP-1) and podoplanin (see arrow). (d) later biopsy (at 2 years) demonstrating BSG particles (see asterick) incorporated into formed lamellar bone trabeculae (see arrow).

CLINICAL OUTCOMES

Radiographs assessment was available for 138 patients, with minimum 1-year follow-up (mean 1.7 years; range 1.0 - 4.7 years).

7 of the 163 (4.3%) cases had infection recurrence, occurring between 0.2- and 2.1-years post-surgery. Recurrence was not significantly higher in C-M IV disease or when plastic surgical soft tissue was used. Calcaneal osteomyelitis was associated with a higher risk of recurrence (2/6 cases (33.3%) compared to 5/132 cases (3.8%)).

The overall fracture rate was 4/163 (2.5%) with a mean time from surgery of 27.5 weeks (range 0.5-13 months). 3 cases occurred due to high-energy injuries and the remaining case was a stress fracture of the proximal femur in an area of previous radiotherapy at 13 months. This case required proximal femoral replacement.

RESULTS

- Infection was eradicated in 95.7% of patients with a single procedure
- Mean bone void filling at final follow-up was 73.8%
- Bone formation continued beyond 2 years in almost two-thirds of patients studied (24/38 patients; 63.2%)
- Histology confirmed active biomaterial remodeling
- Fracture rate was 2.5% (4/163)

CONCLUSIONS

CERAMENT® G is effective in managing dead space in surgically treated patients with chronic osteomyelitis. CERAMENT® G offers a low recurrence rate (4.3%) and good bone void filling (73.8%). Histological analysis supported the radiographic resolution of the bone voids as being associated with bone formation.

Advancing Osteomyelitis Management

- Bone remodeling to protect and promote bone healing
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