Antibiotic Containing Bone Substitute in Major Hip Surgery

A Long Term Gentamicin Elution Study

Stravinskas, Mindaugas; Nilsson, Malin; Horstmann, Peter; Petersen, Michael Mørk; Tarasevicius, Sarunas; Lidgren, Lars

Published in:
Journal of Bone and Joint Infection

DOI:
10.7150/jbji.23901

Publication date:
2018

Document version
Publisher's PDF, also known as Version of record

IVYSPRING INTERNATIONAL PUBLISHER

Journal of Bone and Joint Infection

2018; 3(2): 68-72. doi: 10.7150/jbji.23901

Research Paper

Antibiotic Containing Bone Substitute in Major Hip Surgery: A Long Term Gentamicin Elution Study

Mindaugas Stravinskas[1], Malin Nilsson[2]✉, Peter Horstmann[3], Michael Mørk Petersen[3], Sarunas Tarasevicius[1], Lars Lidgren[2]

1. Lithuanian University of Health, Kaunas, Lithuania
2. Dept of Orthopedics, Lund University Hospital, Lund, Sweden
3. Dept of Orthopedics, Rigshospitalet, University of Copenhagen, Denmark.

✉ Corresponding author: Malin Nilsson, +46 702 688674, malin@lalit.se

Received: 2017.11.17; Accepted: 2018.03.12; Published: 2018.04.12

Abstract

Objectives: The objective is to present the antibiotic elution from a locally implanted gentamicin containing hydroxyapatite and calcium sulphate bone substitute with an extended follow up of 30 days.

We also compare the pharmacokinetics of the ceramic bone substitute with a published study on gentamicin containing poly (methyl methacrylate) (PMMA) bone cement used in primary total hip arthroplasty.

Methods: Gentamicin release was measured in the urine for a month and the serum for 4 days in 10 patients operated for trochanteric hip fractures and 10 patients in uncemented hip revisions. 17 patients were followed up at one year and 3 patients at 6 months.

Results and Discussion: The gentamicin concentrations measured in serum were low and approximately 100 times less than in urine during the first days, indicating high local concentrations at the implant site. The elution from the biphasic bone substitute showed a stronger burst and higher gentamicin concentrations for the first week compared to that reported for PMMA used in hip arthroplasty. Also, for the bone substitute a complete gentamicin elution was obtained after 30 days, while for the PMMA cement sub-inhibitory MIC levels of gentamicin were still present in urine 60 days past surgery. No infections were detected.

Conclusions: A new biphasic bone substitute containing antibiotics could potentially be used to prevent infection in patients treated for trochanteric hip fractures or uncemented hip revisions. The gentamicin elution from the bone substitute is efficient with high initial local gentamicin concentrations and complete release at 30 days.

Key words: bone graft substitute, antibiotics, gentamicin, elution, infection, prevention

Introduction

Local delivery of antibiotics has been shown to be effective in preventing infections in total hip surgery[1]. These patients are often old and more prone to be affected by infections than younger patients groups. The infections cause major suffering impacting the quality of life and generally several surgeries over years, resulting in high societal costs.

This study presents a new bone generating ceramic material which eludes gentamicin to prevent the occurrence of infection while enhancing the bone healing. The product (CERAMENT™|G, BONESUPPORT AB, Lund, Sweden) was developed by adding antibiotics to a clinically well documented bone regenerating biphasic ceramic bone graft substitute[2-5] and it was predicted that the gentamicin would prevent colonization of gentamicin sensitive

organisms in order to protect the bone healing.

This study is an addition to previously short term published data[6] on the gentamicin elution from the biphasic bone substitute CERAMENT™|G. The objective of this new study is to present the gentamicin elution from the same product in major hip surgery over an extended time period, 1 month vs 1 week, as well as to compare this elution with reported release curves from PMMA[7].

Another aim of this study is to show that the local concentration of gentamicin would reach bactericidal level, while the systemic concentration will be well below toxic levels.

Materials and Methods

20 patients underwent hip surgery augmented with a synthetic bone graft substitute (CERAMENT™|G, BONESUPPORT AB, Lund, Sweden). 10 patients with trochanteric fracture were treated with augmented internal fixation and 10 patients underwent augmented uncemented hip revision. The ceramic material was injected after drilling in the distal part of the femoral neck followed by insertion of the sliding screw in trochanteric fractures. In the uncemented revisions a distal anchored stem was used and the ceramic material was injected in the unsupported proximal femoral part. The patient population were 3 men and 17 women with a mean age of 76 years, (±SD 9 years range 57-90y).

The synthetic bone graft substitute consisted of 40wt% hydroxyapatite particles in a calcium sulphate matrix and contained 175mg gentamicin per 10 mL.

None of the patients had systemic gentamicin during the study period.

The patients stayed 7 days at the hospital post-operatively, and both urine and blood serum samples were collected during this time to analyze the gentamicin release from the bone graft substitute.

Urine was collected daily during the hospital stay (7 days) and thereafter approximately every third days for a month. During the first 4 days it was collected from a urinary catheter and thereafter morning urine was collected. The samples were homogenized, transferred into two 50 mL tubes and kept cool in a refrigerator.

Blood serum was assessed every hour for the first 6h post-op and thereafter every 6h (±1h) until 96h post-op (totally 21 samples per patient). A minimum of 4 mL of blood was withdrawn at each time-point and placed in a 5 mL heparin tube. They were centrifuged for 10 min at 2200 x g and the supernatant was transferred to two 5 mL polypropylene tubes and deep frozen at -80°C until analysis.

The gentamicin concentrations in both urine and blood serum were analyzed using a validated antibody technique (QMS® Gentamicin Assay, Indiko™, Thermo Scientific), with a detection limit of the gentamicin concentration of 0.2 mg/L.

Post-op examinations of the patients were performed at 3-6 months and at 1 year. The patients were followed to detect any complications, to observe early loosening of the implants and to study the integration of the material.

The study was approved by the local ethical committee at Lithuanian University of Health, Kaunas, Lithuania (No. BE-2-43) and written informed consent to participate in the study was obtained from all participants.

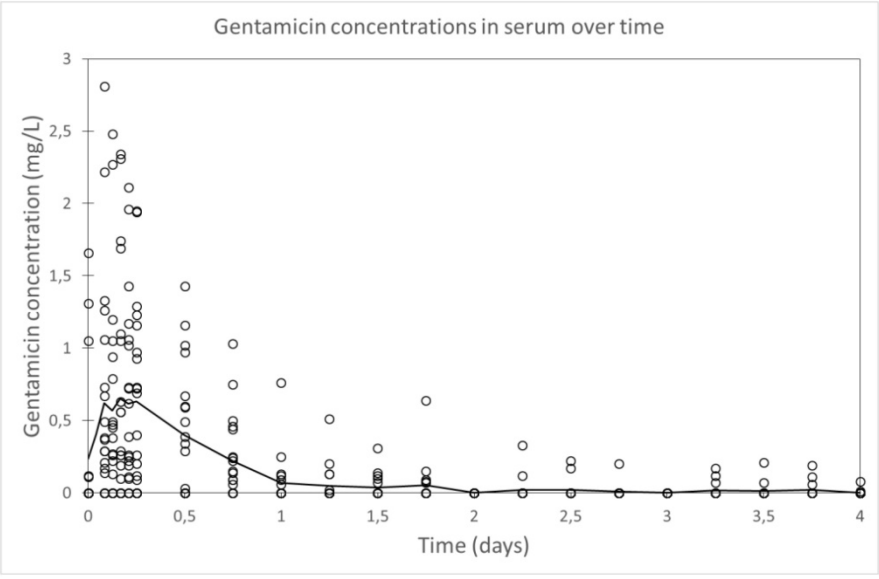

Figure 1: Gentamicin concentrations measured in serum. Every ○ represents one measurement.

Results

The elution of gentamicin from the biphasic ceramic bone substitute had an initial serum peak and then it flattened out after the first days to stay at low levels for the rest of the sampling time (Fig 1). The gentamicin concentrations in the serum was always well below the maximum recommended systemic level of 12 mg/L.

In the urine, the gentamicin concentrations were initially approximately 100 times higher than that in serum. The peak levels were around 100 mg/L and after one week it was still 1 mg/L (Fig 2), reflecting high local

concentrations at the implantation sites. After the first week, the gentamicin concentration in the urine decreased and was maintained at levels below 1 mg/L for the rest of the sampling time. At approximately 28 days, all gentamicin had eluted from the implants (see dotted line in Fig 2).

17 patients were followed for 1 year and 3 patients followed for 6 months; there were no loosening of the revised hips seen during this short follow-up time and no evidence of infection was detected in any of the patients.

Discussion

The elution of gentamicin from the ceramic bone substitute started with an initial burst which decreased mainly during the first week. The elution was followed for 30 days with the aim to present an extended follow-up of already published data in a previous study[6].

The antibiotic concentrations measured in the urine was 100 times the serum concentrations for the first day, which indicate high local concentrations and should allow eradication of any planktonic bacteria causing infection and be effective in preventing bacterial adherence and biofilm production. High local concentrations have also been confirmed and presented in an earlier study[6] where gentamicin concentrations in the wound drainage were measured during the first days post-op.

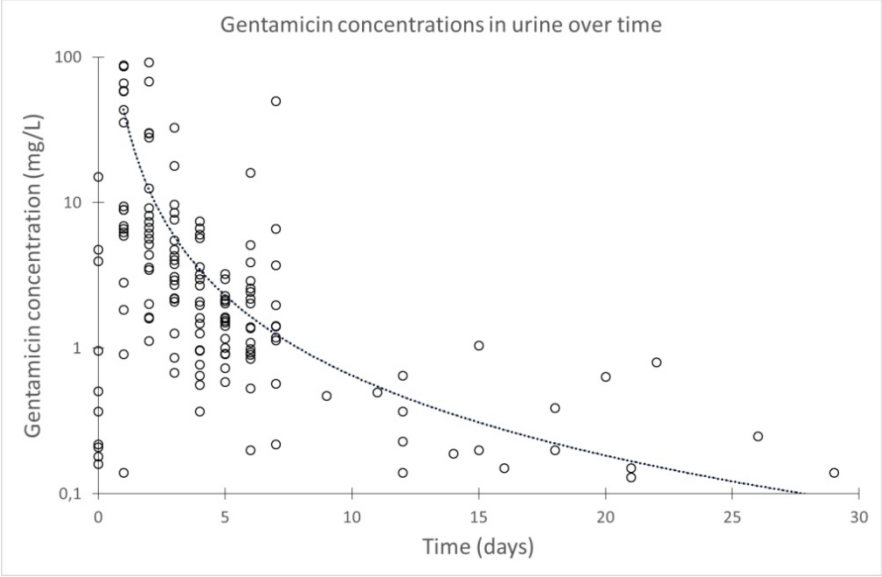

Figure 2: Gentamicin concentrations measured in urine. Every ○ represents one measurement. The dotted line represents the trend line.

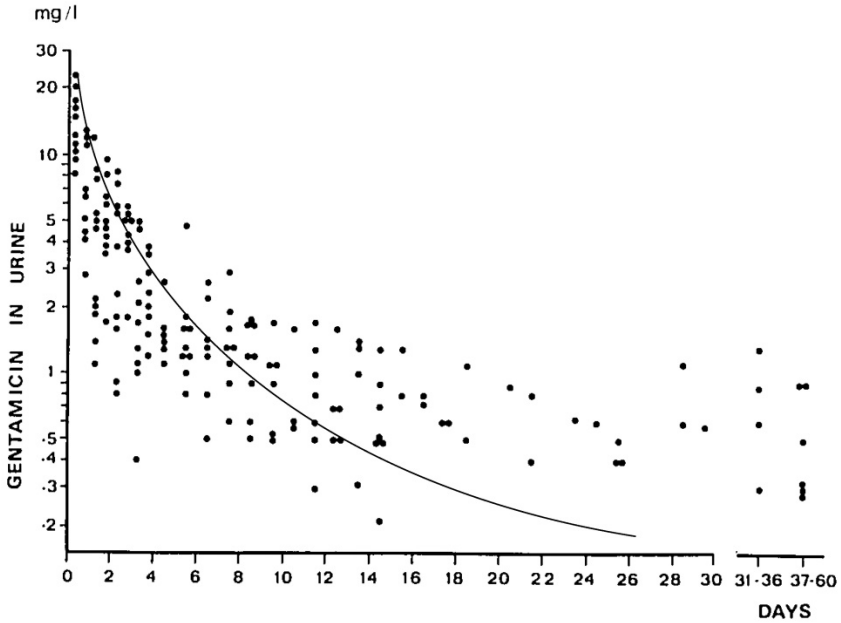

Figure 3: Gentamicin concentrations measured in urine in patients treated with PMMA cements. Figure re-published from Törholm et al.[7] with permission from Wolters Kluwer Health, Inc. The line represents the trend line from Fig 2 for comparison.

Törholm et al.[7] stated that there is a relation between the antibiotic concentration in the urine and the amount of drug available for antimicrobial action at the cement-tissue interface, i.e. locally.

The gentamicin concentration in the urine was detectable for up to 30 days (see Fig 2) which indicates prolonged drug elution in the patients studied. The concentrations decreased following the power function [$y=43.6x^{-1.8}$, $R^2=0.88$] (see dotted line in Fig 2 and solid line in Fig 3) and it shows that almost all gentamicin has been eluted at approximately 28 days. Similar data was published in a previous study where the analysis was based on *in vitro* sampling and complete elution of gentamicin occurred at 28 days[6]. This should be compared to other antibiotic eluting cements, such as PMMA, which entraps the antibiotics with a more prolonged release as a result[7,9-10].

We did comparison with a study performed by Törholm et al.[7] who reported gentamicin concentrations in urine from patients cemented with gentamicin-impregnated PMMA for hip joint arthroplasty. The elution of the gentamicin from the PMMA cement (Fig 3) may appear similar to that of the ceramic bone substitute (Fig 2), with a burst release for the first days followed by a rapid decrease. However, there are large differences. The burst from the ceramic bone substitute is higher with gentamicin concentrations close to 100 mg/L for the first two days compared to maximum 25 mg/L the first day from the PMMA cement. It should also be noted that the mean gentamicin implanted per patient in the PMMA study[7] was 653 mg while 128 mg was reported per patient in the bone substitute study[6]. Hence, despite a higher concentration of gentamicin in the PMMA, it had a significantly lower burst than observed in the bone substitute patients (25mg/L vs 100mg/L).

This may be explained by the nature of the material and the ability for it to elude the antibiotics. The ceramic bone substitute is a porous material, containing approximately 30% microporosity, and the calcium sulphate component resorbs with time in the body[2,5]. It subsequently eludes the antibiotics from both the surface and the bulk which makes it possible for it to completely elude all antibiotics without any residuals being trapped within it. Gentamicin will not bind chemically, nor electrostatically, to hydroxyapatite. Thereby, the complete elution of the gentamicin will be determined by the resorption of the calcium sulphate which normally takes place over 1-2 months[11] but resorption rates as long as 6 months have also been reported for similar materials[12].

In a previous study, it was also shown that the surface area of the biphasic bone substitute did not have any effect on the release rate of the antibiotics[6].

PMMA is a non-resorbing material without significant interconnecting porosity, which means that the antibiotic elusion is mainly occurring from the surface[13]. It is controlled by the surface area of the material and the concentration gradient between the material surface and the surrounding tissue, resulting in a burst followed by a sustained slow and low release[7]. The gentamicin stays entrapped in the PMMA matrix and elutes for years at antibiotic concentrations below the therapeutically level[9,10], and it has been shown that prolonged release at low levels may induce bacterial antibiotic resistance[14]. Other studies have confirmed that antibiotic-loaded PMMA cement reduces infection in total hip replacement but maybe at the price of increasing case specific bacterial resistance[1,15]. Also, severe side effects such as renal failure and ototoxicity have been reported with prolonged gentamicin release, even at low levels, especially if the patient is already suffering from renal insufficiency[16]. It is therefore important to use a material which assures an efficient and complete elution of the gentamicin within a short period of time, i.e. in months.

In Törholm et al.[7], the elution was followed for 60 days at which the gentamicin concentration still was detected at 0.3mg/L. At 2 years, the total amount of gentamicin eluted was estimated to be 275 mg corresponding to 44% of the total gentamycin amount implanted[7].

For the ceramic bone substitute, the gentamicin elution was maintained at significantly higher levels than for the PMMA cement for the first 10 days, with levels dropping from 100mg/L to 1 mg/L over the time period compared to from 25mg/L to 1 mg/L for the PMMA-cement.

The initial urine peak concentration in the gentamicin containing PMMA was significantly shorter and lower despite that 5 times more gentamicin was implanted[7]. But most importantly, after 2 months low sub-inhibitory MIC levels of gentamicin were still measured (see Fig 3).

In summary, the gentamicin elution from the biphasic ceramic bone substitute presented in this study was more efficient than that of PMMA cements due to a higher initial release followed by higher local concentrations for the first week. Moreover, a complete gentamicin elution was obtained for the bone substitute with a minimal risk for bacterial resistance while for the PMMA sub-inhibitory MIC levels of gentamicin were still detectable at 60 days and two years after implantation[7].

The number of patients studied was small and without comparable group, but there were no evidence of infection seen in any of the patients

during the follow-up time. Other studies performed using the same ceramic bone substitute confirm this result, reporting very low rate of recurrence in relapsing long standing osteomyelitis[8].

No loosening of the implants was observed and active integration of the material in the bone healing process could be seen[17].

Conclusions

This study presents a prolonged follow-up of gentamicin elution from a biphasic ceramic bone substitute used for augmentation of internal fixations in trochanteric fractures and of uncemented hip revisions. The gentamicin concentrations were measured for 30 days and gives evidence for an extended efficient antibiotic elution and infection prevention than earlier reported[6].

It shows that the urine concentrations of gentamicin were approximately 100 times the concentration in serum, indicating high local concentrations at the implantation site. Compared to gentamicin containing PMMA[7], the elution was initially higher and maintained at a higher level for the first week. At 30 days, the elution from the biphasic ceramic bone substitute was complete, while sub-inhibitory MIC levels of gentamicin were still detectable at 60 days for the PMMA cement, with a reduced risk of developing bacterial antibiotic resistance with the ceramic material.

Abbreviations

PMMA: poly (methyl methacrylate); MIC: minimum inhibitory concentration.

Acknowledgements

This work was supported by the Swedish Research Council, grant number VR 2015-06717, and Stiftelsen för bistånd åt rörelsehindrade i Skåne, Sweden.

Competing Interests

Prof Lars Lidgren is a member of the board of BONESUPPORT AB and Orthocell Ltd.

References

1. Cancienne JM, Tyrrell Burrus M, Weiss DB, Yarboro SR. Applications of Local Antibiotics in Orthopedic Trauma. Orthop Clin North Am 2015; 46(4):495-510.
2. Abramo A, Geijer M, Kopylov P, Tägil M. Osteotomy Of Distal Radius Fracture Malunion Using a Fast Remodelling Bone Substitute Consisting of Calcium Sulphate and Calcium Phosphate. J Biomed Mater Res B Appl Biomater 2010; 92B:281–286.
3. Karr J. Clinical Case Presentation: Metatarsal Delayed Union Management in a Diabetic Patient with CERAMENT™|BONE VOID FILLER. The Journal of Diabetic Foot Complications 2010; 2(3): 65-68.
4. Iundusi R, Gasbarra E, D'Arienzo M, Piccioli A, Tarantino U. Augmentation of tibial plateau fractures with an injectable bone substitute: CERAMENT™. Three year follow-up from a prospective study. BMC Musculoskeletal Disord 2015; 16:115
5. Nilsson M, Wang J-S, Wielanek L, Tanner KE and Lidgren L. Biodegradation and biocompatibility of a calcium sulphate-hydroxyapatite bone substitute. J Bone Joint Surg [Br] 2004; 86B:120-125.
6. Stravinskas M, Horstmann P, Ferguson J, Hettwer W, Nilsson M, Tarasevicius S, Petersen MM, McNally MA, Lidgren L. Pharmacokinetics of gentamicin eluted from a regenerating bone graft substitute: In vitro and clinical release studies. Bone Joint Res 2016; 5(9):427-35.
7. Törholm C, Lidgren L, Lindberg L, Kahlmeter G. Total Hip Joint Arthroplasty with Gentamicin-impregnated Cement. A clinical study of gentamicin excretion kinetics. Clin Orthop Rel Res 1983; 181:99-106.
8. McNally MA, Ferguson JY, Lau CK, Diefenbeck MD, Scarborough M, Ramsden AJ, Atkins BL. Single-stage treatment of chronic osteomyelitis with a new absorbable, gentamicin-loaded, calcium sulphate / hydroxyapatite biocomposite. A prospective series of 100 cases. Bone Joint J 2016; 98B(9):1289-96.
9. Wahlig H, Dingeldein E. Antibiotics and bone cements. Experimental and clinical long-term observations. Acta Orthop Scand 1980; 52(1):49-56.
10. Neut D, van de Belt H, van Horn JR, van der Mei HC, Busscher HJ. Residual gentamicin-release from antibiotic-loaded polymethylmethacrylate beads after 5 years of implantation. Biomaterials 2003; 24(10):1829-31.
11. Cai X, Han K, Cong X, Cai J, Tong D, Han D, Wang Y, Yu B. The use of calcium sulfate impregnated with vancomycin in the treatment of open fractures of long bones: a preliminary study. Orthopedics 2010; Mar;33(3): DOI: 10.3928/01477447-20100129-17.
12. Fleiter N, Walter G, Bösebeck H, Vogt S, Büchner H, Hirschberger W, Hoffmann R. Clinical use and safety of a novel gentamicin-releasing resorbable bone graft substitute in the treatment of osteomyelitis/osteitis. Bone Joint Res 2014; 3(7):223-9.
13. Walenkamp GH, Vree TB, van Rens TJ. Gentamicin-PMMA beads. Pharmacokinetic and nephrotoxicological study. Clin Orthop Relat Res 1986;205:171-83.
14. Gristina AG, Naylor PT, Myrvik QN. Musculoskeletal infection, microbial adhesion, and antibiotic resistance. Infect Dis Clin North Am 1990;4(3):391-408.
15. Oga M, Arizono T, Sugioka Y. Inhibitition of bacterial adhesion by tobramycinimpregnated PMMA bone cement. Acta Orthop Scand 1992;63:301-4.
16. Nergelius G, Vinge E, Grubb A, Lidgren L. Renal impairment after hip or knee arthroplasty. Urinary excretion of protein markers studied in 59 patients. Acta Orthop Scand 1997;68(1):34-40.
17. Stravinskas M, Tarasevicius S, Laukaitis S, Nilsson M, Raina DB, Lidgren L. A ceramic bone substitute containing gentamicin gives good outcome in trochanteric hip fractures treated with dynamic hip screw and in revision of total hip arthroplasty: a case study. BMC Musculoskeletal Disorders; in press.