The Knee 16 (2009) 39–41

Contents lists available at ScienceDirect

The Knee

Measurements of *in vivo* intra-articular gentamicin levels from antibiotic loaded articulating spacers in revision total knee replacement

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ARTICLE INFO

Article history:
Received 6 May 2008
Received in revised form 28 July 2008
Accepted 28 July 2008

Keywords:
Knee
Arthroplasty
Infection
Antibiotic
Therapy

ABSTRACT

Previous *in vitro* studies have found high levels of antibiotic release in the days immediately following implantation of antibiotic loaded articulating spacers. However there are relatively few data describing the elution profile beyond this immediate period. This study was designed to measure if gentamicin levels continue to be clinically therapeutic after an extended period following *in vivo* implantation.

Twelve patients received a gentamicin loaded articulating spacer between a 1st and 2nd stage revision total knee arthroplasty. At the 2nd stage procedure synovial fluid and blood samples were collected and assayed for the presence of gentamicin.

The second stage revision occurred at a median of 99 days following spacer insertion. The median intra-articular gentamicin levels were 0.46 mg/L (0.24 to 2.36 mg/L) which would be considered therapeutic. There were no cases of reinfection.

In this study, preformed articulating spacers containing gentamicin provided therapeutic concentrations in the synovial fluid surrounding the joint throughout the period of implantation. These data confirm the observations from *in vitro* studies, where a prolonged elution profile was observed for such spacers.

1. Introduction

Knee arthroplasty is one of the most successful procedures for relief of pain and restoration of function in patients with advanced osteoarthritis. Infection of such implants is a recognised complication with rates varying from 1% to 2% and it is associated with considerable morbidity [1,2]. Although the rate of infection of primary knee arthroplasty does not appear to be increasing, worldwide the number of knee replacements continues to rise due to an ageing population and improving access to healthcare in many countries. Therefore the burden of infected prosthetic joints is likely to increase.

A two stage procedure is generally accepted as the most successful method for revising infected total knee replacements [3]. A spacer may be used in the interim to prevent joint contractures, scarring and shortening of the extensor mechanism, as first described by Cohen in 1988 [4]. These can be divided into static and mobile spacers; some are fashioned intraoperatively by the surgeon from bone cement whilst others are purchased preformed.

Antibiotics were first added to the polymethylmethacrylate (PMMA) cement used to fix prosthetic joints in the 1970s [5]. This has been associated with lower rates of infection in primary arthroplasty, though the use of antibiotic containing cement has not been universally accepted. However, the use of antibiotic loaded cement has a much wider acceptance in infection where higher success rates are associated with the use of antibiotic cement for reimplantation of prostheses following infected total knee arthroplasty [3]. Mobile spacers are used in the hope that range of movement is maintained whilst still delivering a local dose of antibiotics.

At present there are relatively good quality data describing the *in vitro* elution profiles of various antibiotics from PMMA cement. However, *in vivo* data to support such *in vitro* data are scarce.

The purpose of this study was to measure the levels of gentamicin in synovial fluid at the 2nd stage revision following the use of a proprietary antibiotic loaded articulating spacer for infected total knee arthroplasty. This has not previously been reported.

2. Patients and methods

Patients were fully counselled prior to surgery and written, informed consent was obtained for the use of samples to be used for research purposes. Twelve patients, with osteoarthritis as their original diagnosis, underwent a two stage revision for infected knee arthroplasty over a 6 month period. The senior author performed both the 1st and 2nd stage operations.

At the first stage, standard procedures were followed and multiple tissue samples were sent for microbiology analysis. This was followed

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doi:10.1016/j.knee.2008.07.009

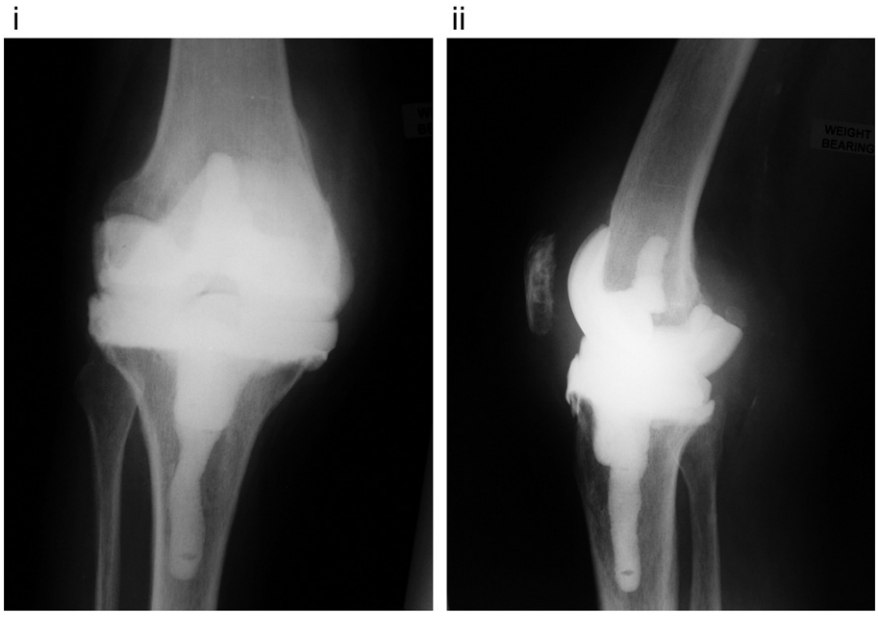

Fig. 1. i: AP radiograph of cemented articulated spacer in situ. ii: Lateral radiograph of cemented articulated spacer in situ.

by removal of the implant and cement and a thorough debridement of all infected tissue and bone. An antibiotic loaded, articulating spacer was then inserted (Spacer K, Tecres, Italy) (Fig. 1). This was cemented in place using antibiotic loaded cement containing gentamicin. No other additional antibiotics were mixed in to the cement. The cement was allowed to cure for 5 min prior to insertion to prevent full interdigitation of the cement into the bone and to reduce the possibility of further bone loss at the 2nd stage. Drains were used routinely and removed at 24 h.

A 14 day regime of parenteral antibiotics followed by a further 4 weeks of oral antibiotics were prescribed at the discretion of the clinician caring for the patient; no patients received further administration of gentamicin. Patients were allowed to mobilise partially weight-bearing in a knee brace locked in extension for mobilisation and encouraged to flex 0–90° as part of their physiotherapy programme when not weight-bearing.

The interval between 1st and 2nd stage revision was recorded. At the 2nd stage revision, venous blood samples were taken for gentamicin assay. At the start of the operation synovial fluid was aspirated from the knee and the gentamicin level analysed as described by White et al. [6]. These samples were taken prior to the incision of the capsule at the 2nd stage procedure since it has previously been shown that gentamicin does not degrade in cement and high levels are measured once the cement mantle is broken [7]. The spacer was then removed without further bone loss where possible. Fig. 2 shows an explanted spacer with the cement mantle intact as a result of careful cementing technique. Patients were followed up postoperatively and assessed for any recurrence of infection.

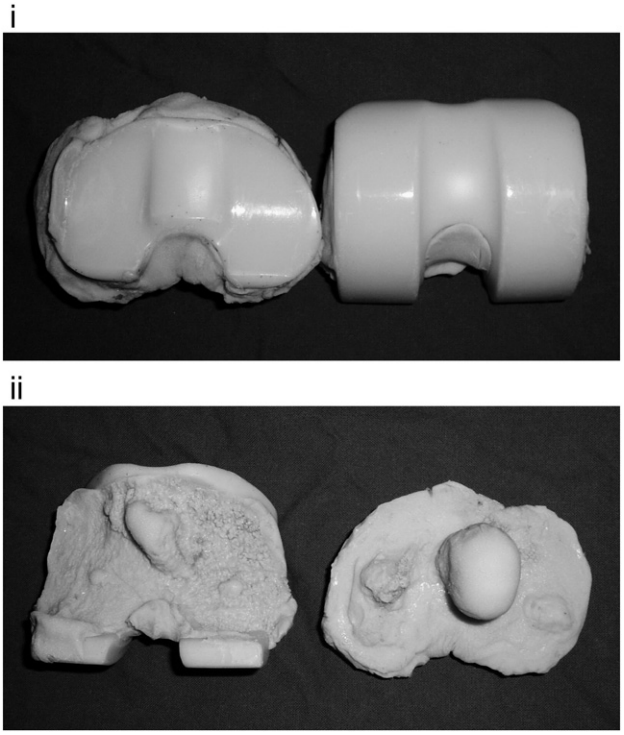

Fig. 2. i: Articulating surfaces of explanted articulating spacer. ii: Bone/cement interface of explanted articulating spacer — note no bone adherent to spacer.

3. Results

There were 12 patients (six men, six women) who underwent a two stage revision over a 6 month period. Their average age was 71 years. A positive microbiology diagnosis was available in all cases. In 10 cases a coagulase negative staphylococcus species was identified, *Staphylococcus aureus* being identified in the other cases.

There was a median interval between the 1st and 2nd stages of 99 days (range 63–274 days). Two implants were left *in situ* longer than initially intended due to patient comorbidity delaying their treatment.

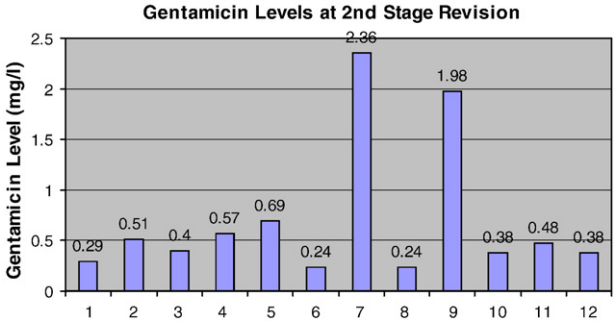

Fig. 3. Intra-articular gentamicin levels at 2nd stage revision for each subject.

Gentamicin was detected in all of the synovial fluid samples, with concentrations ranging from 0.24 to 2.36 mg/L and a median concentration of 0.46 mg/L. These values are shown in Fig. 3.

The concentrations of gentamicin in the blood samples were at or below the limit of detection (0.06 mg/L) in six of the 12 samples and ranged from 0.09 to 0.24 mg/L in the other four samples, with an overall median value of 0.06 mg/L. No correlation could be found between the synovial fluid and blood concentrations of gentamicin (Pearson's Correlation Coefficient 0.117).

At the latest follow up (mean 10 months) no evidence of infection or loosening of the components was identified.

4. Discussion

This study shows detectable intra-articular levels of gentamicin at 3 months following insertion of an antibiotic loaded articulating spacer. Such gentamicin concentrations are above the concentrations needed to inhibit many susceptible pathogens but below the susceptibility breakpoint. The susceptibility breakpoint is the concentration of antibiotic required to kill sensitive strains of bacteria and for the staphylococcal species identified in this series it would be 1 mg/L. These intra-articular antibiotic levels are much lower than one would expect during the first few weeks following implantation and as such may be effective following an initial, higher bactericidal dose. The elution profile of this device has been analysed *in vitro*, showing high early release with 74% of the total antibiotic released in the first week being released in the first 24 h [8]. Previous studies have also shown high early antibiotic release from cement followed by a rapid decrease in release [9,10]. It is therefore interesting to see potentially therapeutic levels of gentamicin at an average of 99 days post insertion of the spacer suggesting that good antibiotic levels are maintained around the spacer for most of the time it is in position. *In vitro* studies have shown dynamically loaded spacers elute more gentamicin than statically or unloaded spacers [11]. Continued release may be due to shear forces as well as cyclical loading of the implant.

These results are largely consistent with the *in vitro* elution study [8], where most release occurred early during the release profile, but suggest that *in vivo* elution may occur over a prolonged period.

There were two outliers with higher levels of gentamicin measured in the intra-articular fluid. No reason could be found for this but it may represent fracture of the cement or spacer. No damage was identified on examination of retrieved spacers.

A weakness of this study is the variable time for the 2nd stage reimplantation. Patients' comorbidities delayed their 2nd stage surgery in two cases. No patients needed a second washout after the initial debridement but the time taken for the inflammatory markers to settle did vary. *In vitro* studies suggest a significant proportion of antibiotic is eluted early so the extra time before the 2nd stage should not have a disproportionate effect on the results. Long term follow up of these patients is required but the absence of infection at the final follow up in this series is encouraging.

The *in vitro* studies showed the antibiotic release did not exceed the recommended maximum daily dose limit of 5 mg/kg/day [12]. The safety aspect of delivering high local doses of antibiotic is reinforced in this study by finding low serum gentamicin levels which did not exceed 0.24 mg/L.

This study shows that an articulating antibiotic laden spacer is effective at delivering therapeutic levels of antibiotic locally in the interim period in two stage revision of infected total knee arthroplasty.

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