Absorbable collagen implants localize delivery of gentamicin in uncemented primary anterior approach total hip replacement

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Absorbable collagen implants localise delivery of gentamicin in uncemented primary total hip arthroplasty

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Abstract

Infection remains a major reason for revision arthroplasty. Localised antibiotic delivery can produce effective concentrations while minimising risks from systemic exposure. Gentamicin-impregnated collagen implants can reduce surgical site infection rates, but orthopaedic usage has been limited.

As a preliminary test of appropriate dosage and safety, we measured local and systemic gentamicin levels after implanting collagen carriers during primary total hip arthroplasty (uncemented, anterior approach), in addition to routine intravenous cephalosporin prophylaxis. The day after surgery, blood samples were taken and wound fluid was sampled from an anaesthetic-infiltrating catheter. Median gentamicin levels were 54.7 mg/l in wound fluid (n=32) and 0.7 mg/l in serum (n=37). Serum levels were all below 2 mg/l; they showed a moderate negative correlation to time elapsed between surgery and sampling, but no significant correlation with local concentrations. No infections or adverse effects were detected over six weeks' follow-up.

These data suggest that delivery of gentamicin to the surgical site via collagen pads achieves high local antibiotic concentrations, with corresponding serum levels within an accepted low-risk range. A single pad produced levels likely to be effective against bacteria associated with infected joint prostheses. Gentamicin-collagen pads may thus provide a useful adjunct to systemic prophylaxis in primary arthroplasty.

Keywords

Antibiotic prophylaxis; Collatamp® G; gentamicin; primary hip arthroplasty; surgical site infection.

Introduction

Postoperative surgical site infection (SSI) is a major complication in arthroplasty, with significant impacts on treatment costs as well as the patient [1, 2]. Although infrequent [2-7], the incidence remains substantial due to the increasing number of arthroplasties performed [8-10]. Infection remains a major cause for revision of hip arthroplasty prostheses across multiple national joint replacement registries [11-19]. The standard prophylaxis currently employed against prosthetic infection is the perioperative administration of an intravenous cephalosporin antibiotic [20, 21]. Although gentamicin is not typically recommended for intravenous antibiotic prophylaxis in hip replacement, gentamicin-impregnated polymethylmethacrylate (PMMA) has proven effective in reducing infection rates in cemented arthroplasty [20, 22-24], particularly upon revision [25, 26]. Through localised delivery, the antibiotics can reach higher concentrations at the surgical site than systemic administration can safely

achieve [27-30]. It is therefore anticipated that local delivery of gentamicin to the surgical site may similarly reduce infection risk in uncemented arthroplasty without compromising safety.

Resorbable collagen matrices allow localised antibiotic delivery in uncemented arthroplasty, without a need for subsequent removal [28, 30]. The rapid and complete elution of gentamicin [31, 32] helps achieve therapeutic concentrations rapidly [31]. In a meta-analysis of 15 randomised controlled trials, prophylactic use of gentamicin-impregnated collagen has been shown to decrease the rate of SSIs [33]. Although this review did not cite orthopaedic applications, usage in sternal closure comprised two-thirds of the cases surveyed, and the sternal wire environment presents similar microbiology to that encountered in arthroplasty [34]. Further reviews and meta-analyses have shown inconsistent results in sternal closure, potentially due to limitations in study sizes and variations in usage [35-41]. Applications in spinal surgery have shown some additional evidence of efficacy in orthopaedics. In one lumbar discectomy study, implantation of a gentamicin-collagen sponge significantly decreased the rate of spondylodiscitis, compared to patients receiving no antibiotic prophylaxis [42]; in another, with exclusively high spondylodiscitis risk patients, it was effective but showed no clear advantage over systemic delivery [43]. Most recently, a small retrospective study demonstrated a decreased SSI incidence across a range of spinal surgery procedures with the use of gentamicin-impregnated collagen, with all patients receiving standard cephalosporin-based prophylaxis [44].

Trials of prophylactic use of gentamicin-collagen implants in arthroplasty procedures have been limited. The only published randomised controlled trial to date showed no difference in SSI rates after hip hemi-arthroplasty in the management of femoral neck fractures, between groups receiving standard antibiotic prophylaxis with or without the additional administration of gentamicin-collagen sponges [34]. In a similar surgical application, the addition of gentamicin-impregnated collagen to prophylaxis corresponded to reduced SSI rates [45], but this was not a clinical trial and it is not possible to separate the contributions of each component of the care package to the outcome observed. The first reported use of gentamicin-collagen implants in orthopaedic surgery was as prophylaxis in joint replacement [46], but no outcomes were given for these cases and no subsequent follow-up appears to have been published. To date, antibiotic concentration data have not been adequately reported for gentamicin-collagen prophylaxis in total hip arthroplasty. Ascherl et al. [46] reported only serum gentamicin levels for one uncemented arthroplasty patient: these remained below 0.5 mg/l from day 1, after implantation of a collagen sponge containing 120 mg gentamicin (equivalent to 1.8 mg/kg dose).

Although the use of gentamicin-collagen sponges in primary total hip arthroplasty (THA) has been reported [47], appropriate dosages, efficacy and safety have not yet been verified for this application. In addition, collagen implant degradation and the related antibiotic delivery profile may depend on variations in both the anatomic site of administration and surgical approach. We report gentamicin levels in the wound fluid and serum following the administration of single Collatamp G implant in uncemented THA conducted via a direct anterior approach.

Material and methods

Between October 2014 and February 2015, 39 patients (42 hips) were treated by conventional total hip arthroplasty via a modified Hueter anterior approach with co-administration of a single gentamicin-impregnated collagen implant (Collatamp® G, Syntacoll GmbH, Saal/Donau, Germany) as an adjunct to standard antibiotic prophylaxis. Osteoarthritis was the indication for surgery in all cases. No patient had a history of renal disease or demonstrated dysfunction on preoperative blood testing.

Prior to surgery patients were instructed to wash daily with Phisohex 1% (Hexachlorophene; Sanofi-Aventis, Bridgewater NJ, USA) for five days (or Chlorhexidine 2% if unsuitable). All patients underwent surgery by the administration of general anaesthesia, without the use of regional or spinal block. Intravenous antibiotic prophylaxis consisted of Cephazolin 2g administered prior to induction in all patients (Kefzol, Aspen Pharmacare, Australia).

All procedures were conducted via an anterior approach (without traction) using a low bikini line incision with retention of the anterior capsule. Uncemented acetabular and femoral implants were used for all procedures. A mixture of 150 ml Ropivacaine 0.2% (Naropin, AstraZeneca, North Ryde, NSW, Australia), Ketorolac 30 mg (Toradol, Roche Products, Dee Why, Australia) and 0.5 ml Adrenaline 1:1000 was infiltrated into both the deep and superficial tissues during the procedure for analgesia.

After repair of the anterior capsule during wound closure, a single Collatamp G implant (100×100 mm, 200 mg gentamicin sulphate, equivalent to 130 mg gentamicin) was placed within the deep wound space in an extracapsular position beneath the tensor fascia lata (Figure 1). Adjacent to the Collatamp G implant, also within the deep wound space, a 19G multi-hole saturation catheter (Moog Medical Devices Group, Salt Lake City, USA) was placed for subsequent post-operative local anaesthetic administration. A single patient was managed with a 10Fr wound drain due to excessive bleeding associated with anticoagulant use (data from this patient has been excluded from this study). Post-operative antibiotic prophylaxis included intravenous Cephazolin 1 g administered at 8-hourly intervals, discontinued within 24 hours of the procedure.

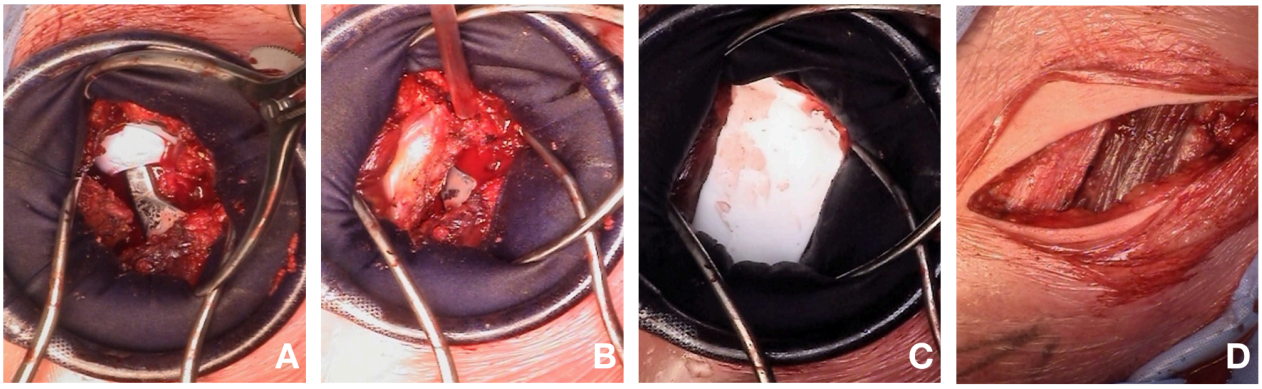

Figure 1: Placement of the Collatamp G sponge during left anterior approach total hip replacement. After repair of the anterior capsule over the definitive implants (*A-B*), a single 100 mm × 100 mm Collatamp G sponge is placed upon the anterior capsule within the deep wound space beneath the tensor fascia lata layer (*C-D*).

Gentamicin Level Sampling

For post-operative analgesia, it has been our standard practice to infiltrate a bolus dose of 40 ml Naropin 0.2% into the extra-articular deep tissue space via the saturation catheter placed during surgery at 8:00 a.m. on the first post-operative day. To enable sampling of the deep space fluid for subsequent gentamicin level analysis in this study, two 5 ml aspirates were taken from the saturation catheter prior to infiltration of the local anaesthetic. The first 5 ml of aspirated fluid was discarded. The second 5 ml aspirate was retained as a representative sample of the fluid within the periarticular deep wound space and subsequently placed within an appropriate drug assay blood collection tube (plain) and sent for analysis. Venous blood was simultaneously obtained at the time of wound aspiration for subsequent gentamicin level analysis and tested for serum gentamicin level. Serum and wound aspirate gentamicin concentrations were conducted by Sullivan Nicolaides Pathology (Queensland, Australia). After wound catheter aspiration, the bolus local anaesthetic infiltration was conducted followed by catheter removal.

Statistics

Statistical calculations were performed using SPSS Statistics (Version 23 for Macintosh, IBM Corp., Armonk, NY). Correlations were tested between wound fluid and serum gentamicin concentrations, and between each concentration and the time elapsed between surgery and sampling. For analysis, concentrations below the detection limit (0.1 mg/l) were taken as zero. To remove the potential influence of implanting a second Collatamp G pad, bilateral THA patient data (3 patients) were excluded from testing the correlations between the two concentrations, and between sampling time and serum levels. Both Pearson (r) and Spearman (r_s) correlation coefficients were calculated. Because data showed increased deviation from a normal distribution at the highest concentrations (Q-Q plots), Spearman correlations are reported as the more reliable indication (Shapiro-Wilk tests for serum levels: $p = 0.23$ and 0.44 for all unilateral patients and only those with wound fluid samples respectively; and for wound fluid levels: $p < 0.001$ and 0.14, for all samples and unilateral only, respectively).

Ethics

This research activity has received Institutional Review Board approval from the Uniting Health Care Health Research Ethics Committee (Queensland, Australia), and was conducted in accordance with the World Medical Association Declaration of Helsinki.

Results

Serum gentamicin levels were obtained for all but one patient. Wound fluid aspirate samples were successfully obtained from 33 hips. One patient was excluded due to placement of a wound drain. Of the patients where no wound fluid aspirate was obtained, no sampling was attempted for two patients and no fluid could be obtained from seven wounds (dry tap). Where fluid could be obtained from only one hip of bilateral THA patients (2/3), the results of the wound levels are included in our data. We therefore report upon 37 serum and 32 wound fluid results.

The median concentrations of gentamicin were 54.7 mg/l (range: 6.0–315.8 mg/l) in wound aspirates and 0.7 mg/l (range: <0.1–1.8 mg/l) in serum. Excluding bilateral THA patient data did not alter the median or range of values for serum gentamicin, although with only three of these patients, a valid statistical comparison could not be made. A local wound concentration below 8 mg/l was only measured in one patient, with a further two hips yielding samples just below 20 mg/l gentamicin (one in a bilateral THA patient, whose other wound aspirate showed 79.8 mg/l). Twenty-five wound aspirates measured >32 mg/l gentamicin.

The time elapsed between surgery and sampling showed a moderate negative correlation with serum

gentamicin concentrations (r_s = –0.50, p = 0.003, n = 34). The correlation between wound aspirate gentamicin level and the time interval was not significant (r_s = –0.26, p = 0.15, unilateral + bilateral, n = 32). The correlation between the local and serum concentrations was weak (r_s = 0.36, p = 0.06, n = 28) and significant only by the Pearson test (r = 0.38, p = 0.05), excluding bilateral THA data.

All procedures were completed successfully and no infections or adverse effects were identified post-operatively or over six weeks' follow-up.

Discussion

Consistent with previous clinical studies [28, 48-54], the use of gentamicin-impregnated collagen pads in this case series resulted in consistently high concentrations within the local wound, without associated excessive serum levels. Within 24 hours of surgery, all serum gentamicin levels were below 2 mg/l, while concentrations at the surgical site remained high (only one sample below 8 mg/l). No adverse effects were observed and no infections have been detected to date among the patients treated.

This report also introduces the use of an anaesthetic infiltrating catheter for wound fluid sampling. This approach was successful in 33 of 41 attempts, and avoided the need to alter surgical practice in order to monitor local gentamicin levels.

Efficacy of delivery method

Clinical studies have confirmed that implantation of gentamicin-collagen sponges/pads produce high early levels of antibiotic within tissues (in the order of 300 mg/l), while maintaining low serum concentrations [28, 48-54]. Although similarly high in comparison to serum concentrations, the local wound gentamicin levels observed in this study are lower than described in most gentamicin-collagen clinical reports to date [28, 48-56]. This may be attributed to differences in sampling time as well as dosage and the surgical procedure.

Although our study showed little correlation between wound fluid gentamicin levels and time elapsed since surgery, local concentrations have been shown to peak within the first 12 hours after implantation, decreasing substantially over the first 24 hours [28, 48, 49, 53, 54, 56]. In the present study, samples were drawn between 14 and 24 hours after surgery (median 19 hours). Friberg et al. [48] showed that the median concentration peaked at 304 mg/l after two hours, then dropped below 50 mg/l by 12 hours (2 × 130 mg sponges). Jørgensen et al. [54] showed a decline of more than 90% in the first 12 hours, reaching 80 mg/l by 24 hours after implantation of one collagen sponge. Many of the previously reported applications have used multiple collagen carriers. Conversely, local gentamicin concentrations after application of a single carrier are of a similar order to those reported here [31, 54, 55].

Gentamicin concentrations at the surgical site associated with the use of a biodegradable collagen carrier depend both on the anatomical location and the tissue vascularity [50]. Feil et al. [55] found substantially lower levels in wound fluid from infected hip arthroplasty than from other bone infection sites after treatment with gentamicin-collagen implants. The degree of surgical trauma may also influence elution and distribution [57]. Furthermore, concentrations are expected to steeply diminish with distance from the carrier [58], although the distance between the collagen carrier and sampling catheter had no significant impact on pharmacokinetic data in a gentamicin distribution study [57]. To our knowledge, this is the first report of local gentamicin levels after the application of Collatamp G or similar products in hip arthroplasty. However, the range of concentrations from 6–316 mg/l (median 54.7 mg/l) are comparable to those reported for other applications at a similar time-point and/or dosage, and peak levels may be expected to have been significantly higher than measured within this study.

While the position of the Collatamp implant was extracapsular, we consider achieving high gentamicin levels within the deep space of the surgical wound to be a useful strategy for the overall reduction in infection risk associated with hip arthroplasty surgery. In addition, as the capsular closure is incomplete, gentamicin levels observed within the extra-articular deep space are likely to approximate those found within the capsular space surrounding the joint replacement.

As with local concentrations, it is likely that serum levels had peaked prior to sampling and would continue to decline subsequently. Where previously reported, serum gentamicin peaked by 12 hours after implantation of collagen carriers in the majority of cases [31, 48, 49, 51, 53, 54, 56, 59-61]. The detected range of <0.1–1.8 mg/l (median 0.7 mg/l) is comparable to the 0.5–1 mg/l range expected 14 hours after intravenous or intramuscular administration of a single daily dose of gentamicin, and to the required daily trough levels of <0.5 mg/l [62]. It is also consistent with the serum levels reported by Ascherl et al. [46], from 24 hours after implantation of a gentamicin-collagen sponge in uncemented arthroplasty.

Although three patients are too few to allow statistical comparison, the range of results did not suggest that bilateral use of Collatamp G increased serum gentamicin levels beyond those measured after unilateral application (0.2–1.7 mg/l for bilateral THA patients vs <0.1–1.8 mg/l for unilateral). A previous report showed no correlation between the number of collagen carriers implanted and serum gentamicin concentrations [61]. However, toxic levels were only reported by the same group when 4–6 sponges were applied [63], and lowest serum levels in an early study were found in patients receiving only one sponge [51].

Comparison with other delivery methods

As mentioned above, gentamicin-impregnated bone cement has proven effective in arthroplasty [20, 22-26]. In uncemented arthroplasty, antibiotics may be delivered locally via implant coatings, PMMA beads or collagen matrices. While coated implants may be beneficial in fracture fixation [64], secondary antibiotic coating of arthroplasty prostheses [65] has not progressed to commercialisation for routine use in primary joint replacement. Local administration of antibiotics by implanting PMMA beads has the disadvantage of requiring subsequent surgical removal [29]. In addition, the sustained presence of sub-therapeutic levels of gentamicin released from PMMA [52, 66] may also favour the development of resistant strains of bacteria [67-69], and colonisation of the polymer surface by one microorganism may facilitate adhesion of other pathogenic species [70]. Although smaller beads allow more rapid and complete elution [71], retrieval studies have shown substantial gentamicin quantities retained in PMMA beads over several months [66]. After ~12 months of implantation, PMMA beads have been found to retain 32–46% of their original gentamicin content with sub-therapeutic levels in the surrounding tissue [52].

In contrast, collagen matrices minimise the PMMA-associated risks by rapidly and completely releasing the gentamicin [31, 32] and being fully biodegraded. The high local concentration initially, steeply declining after the first few days, is consistent with a relatively rapid, near-complete elution of gentamicin from collagen sponges over the first two weeks after implantation [50, 51, 54]. In vitro elution testing shows a similar advantage, with 95% of the gentamicin released from collagen within hours [72].

Efficacy of local gentamicin prophylaxis

Although our focus is on prophylaxis, the chief orthopaedic use of gentamicin-collagen implants has been in the treatment of periprosthetic and other bone infections. Although successful in this application [28, 46, 49, 52, 55, 59, 73-76], few controlled trials have been published. In two studies showing that treatment with gentamicin-collagen resulted in fewer re-operations than gentamicin-PMMA implants [56, 77], only the larger study showed an actual reduction in infection eradication, and only in the short term [77]. Although better outcomes were described for treatment of post-operative shoulder infections with gentamicin-collagen pads [78], these were placed as part of an arthroscopic procedure, while the comparison cohort was treated by an open procedure in which an unspecified proportion received gentamicin-impregnated PMMA beads. Geurts et al. [79] presented a retrospective study of peri-prosthetic infection treatment, involving local delivery of gentamicin, but their reported outcomes did not differentiate between the application of PMMA and/or collagen carriers. Collagen carriers have also been effective in gentamicin release and prevention of infection after fracture fixation [31, 80], but neither of these articles presents a controlled trial.

The bacteria most commonly isolated from arthroplasty-associated infections are gram-positive, chiefly *Staphylococcus aureus* and c*oagulase-negative staphylococci* (CoNS, particularly *S. epidermis*) [8, 9, 34, 52, 69, 81-85]. Many strains of these, including strains isolated from revision arthroplasty and osteomyelitis, have been identified as resistant to gentamicin [8, 9, 28, 52, 55, 69, 83, 86], being an antibiotic which is primarily active against gram-negative bacteria. More than 40% of CoNS strains were gentamicin resistant in multiple arthroplasty studies [8, 9, 69] and their resistance has shown an increase over time [83]. Nonetheless, there are several indications for the inclusion of gentamicin in perioperative prophylaxis:

- Through localised delivery, gentamicin can reach sufficiently high concentrations to be effective against even organisms considered resistant [28, 48, 49, 52, 58], due to the rate of bactericidal activity exceeding that of enzymatic inactivation [52];

- Aminoglycosides such as gentamicin act synergistically with the cell-wall-disrupting β-lactam antibiotics (including cephalosporins) against gram-positive bacteria [21, 87, 88];

- Many strains of *staphylococci* (especially *S. aureus*) are sensitive to gentamicin [89], including organisms isolated from arthroplasty [9, 66], and a trend of increasing sensitivity among methicillin-resistant *S. aureus* was recognised in the 1990s [90];

- Gram-negative bacilli also pose a risk in orthopaedic procedures [82]. Early prosthetic infections in particular (<3 months after surgery) have been associated with more virulent microorganisms including gram-negative bacteria and *S. aureus* [91], although this trend is not always observed [8, 92].

Aminoglycoside bactericidal effectiveness is concentration-dependent [87], and it is important to consider that sensitivity and target plasma concentrations are defined with respect to systemic antibiotic administration [93-95]. The degree to which their concentration exceeds the minimum inhibitory concentration (MIC) for a microorganism has been associated with clinical efficacy [96] and preventing the emergence of resistance [97]. Although peak plasma concentration targets of 8–10 times MIC are generally recommended [94, 95, 97], the local availability of the antibiotic at the surgical site determines its efficacy [98]. The peak concentration is lower locally than in the bloodstream after systemic delivery [50, 98-100], and this may be further reduced by factors such as the reduction of blood supply to a tissue by trauma or infection [101, 102]. A local concentration above 8 mg/l (often considered the cut-off MIC for defining resistance) is, however, readily achieved via implanted carriers [28, 58, 79]. Levels thus achieved have been shown to exceed MICs for most bacteria classified

gentamicin resistant, including *S. aureus* and *CoNS* [28]. All but one wound aspirate in our series showed gentamicin above this concentration.

In one study of local gentamicin delivery in treatment of hip and knee periprosthetic infections, sensitivity testing showed that 82% of isolated bacteria were inhibited by gentamicin concentrations ≤8 mg/l and 94% were inhibited by 64 mg/l [79]. Among *S. epidermis* strains isolated from infected hip prostheses, half were inhibited by 16 mg/l gentamicin; to inhibit 90% of isolates required 256 mg/l [69]. In the same study, most other *staphylococci* (including *S. aureus*) were inhibited by 32 mg/l gentamicin or less. In contrast, tests of 157 *CoNS* strains defined as gentamicin resistant showed that 89% were inhibited by 32mg/l and 98% by 64 mg/l [28]. The same study showed that, among 90 strains of gentamicin resistant *S. aureus*, 79% were inhibited by 32 mg/l and 93% by 64 mg/l [28]. Given that the local gentamicin concentrations reported in this case series likely underestimate the peak level, efficacy against the majority of prevalent bacteria in arthroplasty-associated infections seems likely. It must be emphasised that this estimation of efficacy applies to primary arthroplasty, and not treatment or revision of infected prostheses.

Minimising aminoglycoside toxicity risks

In contrast to systemic administration, local delivery of an antibiotic theoretically allows effective concentrations where they are needed, with both lower serum levels and an equivalent or lower overall dosage. Aminoglycosides such as gentamicin carry the risk of nephrotoxicity and otovestibular toxicity [87, 103]. While no safe levels have been identified to avoid the latter [104-106], nephrotoxicity has been associated with sustained treatment (more than 5–7 days), pre-existing renal impairment and minimum daily (trough) serum gentamicin levels over 1.1 mg/l [21, 107, 108].

When indicated for prophylaxis, an intravenous gentamicin dose of 2–5 mg/kg is recommended [21]. Hence, implanting one Collatamp G pad (200 mg gentamicin sulphate = 130 mg gentamicin) typically represents a lower total exposure than a standard prophylactic or therapeutic intravenous dose. Ruszczak and Friess [50] report that no side-effects were detected in over one million patients treated with gentamicin-collagen sponges; however, this claim is not well supported by the level of detail presented (cohort and assessment details are summarised for only selected studies). Although Swieringa et al. [63] describe a series of patients treated with gentamicin-collagen sponges exhibiting high-risk serum concentrations (3–13 mg/l, mean 4.3 mg/l) and impaired renal function, a relatively large number of sponges (4–6) were used at the infection site, and correlation between serum gentamicin concentration and reduction in creatinine clearance was not demonstrated. A later study by the same research group, using fewer sponges, found all serum levels below the defined toxic threshold (2 mg/l) by 24 hours and only transient reduction in creatinine clearance in 2/19 patients [61]. A transient elevation of serum creatinine in 4/34 patients was reported in one other study [73]; no other adverse effects were reported in the gentamicin-collagen studies cited above. Across these other clinical studies, mean/median peak serum levels did not exceed 12 mg/l (most <4 mg/l) and, similar to our results, fell below 2 mg/l by 24 hours [28, 48-51, 53, 54, 56, 60, 109]. Where reported, serum levels were below 1 mg/l by 48 hours after implantation [46, 48, 51, 53, 56, 61, 63]. In contrast, there is some evidence that sustained serum gentamicin from PMMA beads (≥0.4 mg/l at 7 days) corresponds to a greater likelihood of nephrotoxicity [110].

Our measured serum concentrations fall within the range expected from standard gentamicin dosing and are therefore considered to pose minimal risk of nephrotoxicity. Additionally, not delivering this directly into the bloodstream may be expected to minimise exposure of non-target systems and tissues.

Conclusion

Although preliminary, the data from this case series indicate that a Collatamp G pad implanted in the periprosthetic wound space achieves high local gentamicin levels, with serum levels within the accepted low-risk range, after primary anterior approach total hip arthroplasty. Comparison of local concentrations to the minimum inhibitory concentrations for relevant bacteria suggests that a single pad is sufficient for this application. Although awareness of vestibulotoxicity risks and testing methods, and measurement of serum concentrations, are advised, it is anticipated that localised delivery minimises the risks associated with gentamicin use. Implantation of Collatamp G was convenient, and may constitute a useful adjunct to standard β-lactam prophylaxis in total hip arthroplasty.

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Conflicts of interest statement

The authors certify that they have no affiliations with or involvement in any organisation or entity with any financial interest, or non-financial interest in the subject matter or materials discussed in this manuscript.

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