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CLINICAL RESEARCH

What is the Intraarticular Concentration of Tobramycin Using Low-dose Tobramycin Bone Cement in TKA: An In Vivo Analysis?

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Abstract

Background Antibiotic-impregnated bone cement has increased in popularity as an effort to reduce the risk of infection in high-risk TKAs. However, limited data has been reported regarding antibiotic levels achieved when using tobramycin-impregnated bone cement after implanting total knee components.

Questions/Purposes We asked: (1) What is the tobramycin serum and knee intraarticular levels in patients undergoing primary TKA using tobramycin cement? (2) What is the intraarticular tobramycin level for patients receiving only intravenous tobramycin?

Methods All patients undergoing primary TKA by one of the two study surgeons (GV, JP) during a 6-month period were evaluated for inclusion and invited to participate. The study enrolled 15 patients undergoing primary TKA by one of two surgeons (GV, JP) who met inclusion criteria; treatment allocation was assigned randomly through blinded envelope. The study group consisted of 10 patients whose components were implanted using a commercially prepared low-dose tobramycin bone cement mixture (1 g/40 g). The control group consisted of five patients who received standard weight-based dose intravenous tobramycin. Samples of serum and Hemovac® drain-collected intraarticular hematoma were analyzed at 6, 24, and 48 hours postoperatively. Tobramycin levels were measured using an immunoassay technique with a low-end sensitivity of 0.28 μg/mL. Mann-Whitney U tests were performed to compare the serum and intraarticular tobramycin concentrations at each time in the independent variable of group (Control and Study).

Results The median (interquartile range [IQR]) intraarticular tobramycin concentrations for the study group, with tobramycin-impregnated bone cement, was 31.8 (29.0) μg/mL at 6 hours, 17.1 (13.1) μg/mL at 24 hours, and 6.8 (6.8) μg/mL at 48 hours. The intraarticular tobramycin concentrations of this study group were larger than those for the control group at 6 hours (median = 1.3; IQR = 0.7; $p = 0.002$), 24 hours (median = 1.3, IQR = 1.0; $p = 0.002$), and 48 hours (median = 1.4; IQR = 1.0; $p = 0.02$). The serum concentrations for the tobramycin-impregnated bone cement group were 0.3 μg/mL or less for all samples whereas serum concentrations and median (IQR) for the control group were 1.2 (2.6) μg/mL, 1.6 (4.4) μg/mL, and 2.0 (3.3) μg/mL at 6, 24, and 48 hours respectively. The serum levels for the tobramycin-impregnated cement group were less than those for the control group at 6 hours ($p = 0.001$), 24 ($p = 0.001$), and 48 hours ($p < 0.001$).

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Conclusions Tobramycin-impregnated bone cement provides a way to deliver antibiotics in patients undergoing TKA. This supratherapeutic short-term prophylactic perioperative antibiotic local delivery can be achieved with limited systemic absorption, whereas joint tobramycin levels were less than therapeutic levels when given intravenously alone. In the control group, with only intravenous tobramycin, a subtherapeutic (< 2.0 μg/mL) level of tobramycin was found in all the intraarticular samples at 6, 24, and 48 hours. Based on the evidence obtained in this study, commercially prepared low-dose tobramycin bone cement can be used to obtain short-term supratherapeutic local concentrations in the knee while maintaining serum tobramycin levels at a minimum.

Level of Evidence Level II, therapeutic study.

Introduction

Antibiotic-laden bone cement has been a mainstay in the treatment of prosthetic joint infection of the hip and knee for many years [4, 10], and more recently, particularly in Europe, it has been used increasingly in primary arthroplasties, where its use has been associated in a registry study with reductions in the risk of prosthetic joint infection [6].

The pharmacokinetics of tobramycin cement in primary total hip replacements have been studied [21], however the pharmacokinetics of tobramycin cement in primary total knee replacements, to our knowledge, have not been reported, and thus provided the motivation for our study. This is in contrast to the standard use of systemic intravenous prophylactic antibiotics routinely used in joint replacement surgery [4]. Initially, antibiotic-impregnated bone cement was used solely in explant revision surgery to treat infections in patients who underwent arthroplasty [9]. In this role, high doses of antibiotics were delivered via the cement after mixing (> 3.6 g per 40 g bone cement). Low-dose antibiotic-impregnated bone cement (0.5–1 g per 40 g of cement) is available as a commercially preblended product [21]. Although widely accepted in Europe, in the United States, the use of antibiotic-impregnated bone cement has been reserved for reimplantation in patients with previous infection or at high risk attributable to immunocompromising comorbidities [6, 22]. Advantages of this approach include consistent elution of locally high operative-site antibiotic concentrations for infection prophylaxis or treatment, while producing minimal systemic antibiotic levels. A meta-analysis of antibiotic-impregnated bone cement used in primary THAs or TKAs found that antibiotic-impregnated bone cement could decrease the deep infection rate compared with controls, but had minimal effect on superficial infections [24].

A 1995 survey of 1015 orthopaedic surgeons in the United States found that of the 56% who used antibiotics in bone cement, 70% used tobramycin [10]. Tobramycin has been shown to be an excellent drug for addition to bone cement, because it has low antigenicity, is well tolerated in humans, and has a broad spectrum of antimicrobial activity including aerobic gram-negative bacilli and *Staphylococcus aureus* [10, 19, 20, 22]. Tobramycin retains bioactivity through the exothermic bone cement polymerization process and displays favorable elution kinetics in vitro [1, 7, 15]. Low-dose tobramycin-impregnated bone cement has been shown to not substantially compromise the mechanical integrity of bone cement [5, 14]. Tobramycin-impregnated bone cement has been shown in vivo to produce supratherapeutic (> 2.0 μg/mL) wound hematoma levels in patients who underwent THA [20, 21]. These same principles and techniques are applied to TKA, although, to our knowledge, tobramycin levels achieved after implanting knee components using tobramycin-impregnated bone cement have not been reported.

We therefore asked: (1) What are the tobramycin serum and knee intraarticular levels in patients undergoing primary TKA using tobramycin cement? (2) What is the intraarticular tobramycin level for patients receiving only intravenous tobramycin?

Methods

Study Design, Patient Enrollment, and Demographics

The protocol for this study was approved by the institutional review board of our institution. All patients undergoing primary TKA by one of the two study surgeons (GAV, JLP) during a 6-month period from January through June 2002 were evaluated for inclusion and invited to participate. While this data is more than 10 years old, the study question still had not been addressed in the intervening years by any other investigation and formed the basis for a future study we have initiated. There were no special indications for the use of tobramycin in this setting (such as preexisting infection, revision surgery, or other comorbidities); this was a study intervention. Likewise, closed-suction drains were used to gather the needed data in this study. All of this was approved in advance by the institutional review board, and discussed before enrollment with all patients as part of the informed consent process. To minimize overall risk, we kept the study number as small as we reasonably could based on our prior estimates of effect size used in our statistical power calculations.

Patients with known aminoglycoside hypersensitivity or who had received tobramycin during the previous month were excluded from the study. Patients with contraindications to the use of tobramycin, including renal disease, myasthenia gravis, hearing deficits, Parkinson's disease, liver disease, or blood dyscrasias, also were excluded. Demographic information, body weight, and diagnosis were documented for each patient enrolled in the tobramycin-impregnated bone cement group (Table 1) and the intravenous tobramycin group (Table 2). Fifteen patients were enrolled in the study and randomly assigned by blinded envelope. One group consisted of 10 patients whose components were implanted with a commercially prepared low-dose tobramycin bone cement mixture (1 g/40 g). The other group consisted of five patients who received a weight-based dose of intravenous tobramycin only and plain Simplex™ cement (Stryker® Howmedica Osteonics; Mahwah, NJ, USA). Using Mann-Whitney U tests, it was determined that the two groups did not differ with respect to age ($p = 0.666$) or weight ($p = 0.624$). In addition, with Fisher's exact test it was determined that the two groups did not differ with respect to gender distribution ($p = 0.329$). Samples of serum and intraarticular hematoma were collected at 6, 24, and 48 hours postoperatively. Tobramycin levels were measured using an immunoassay technique with a low-end sensitivity of 0.28 μg/mL. Patients were followed by the operating surgeon (GAV, JLP), with final study followup at one year.

Description of Experiment, Treatment, or Surgery

Ten patients had TKA components implanted with a commercially prepared low-dose tobramycin and bone cement mixture (Simplex™ P with Tobramycin; Stryker Howmedica Osteonics). The preblended mixture contained 1 g of tobramycin with 40 g of bone cement. The weight of the cement mixture used and component size were recorded for every patient in the tobramycin-impregnated bone cement group. All patients had the same brand of components implanted so that sizes could be accurately compared (Genesis™ II Total Knee System; Smith & Nephew; Memphis, TN, USA). When patellar resurfacing was performed this also was documented. A group of five patients received intravenous tobramycin only. A weight-based loading dose of 1.5 mg/kg was administered preoperatively, followed by 1 mg/kg every 8 hours for 48 hours. Serum tobramycin levels were monitored but dosing was not adjusted owing to the rapid urinary excretion rate of the medication in patients with normal renal function. The cement used in the control patients did not contain any antibiotics (Simplex™ P). All patients had intraarticular Hemovac® drains (Zimmer Biomet, Warsaw, IN, USA)

Table 1. Patient data for the tobramycin-impregnated bone cement group

Patient	Age (years)	Gender	Diagnosis	Weight (kg)	Cement weight (g)	Component size femoral/tibial	Patella	Prophylaxis	6 hours (μg/mL)	Serum 24 hours (μg/mL)	48 hours (μg/mL)	6 hours (μg/mL)	Intraarticular 24 hours (μg/mL)	48 hours (μg/mL)
1	57	F	OA	92.1	22.4	5/3	No	Cefazolin	< 0.3	< 0.3	< 0.3	11.3	2.9	1.2
2	59	F	OA	112.5	26.2	6/5	Yes	Cefazolin	0.3	< 0.3	< 0.3	43.5	22.9	9.5
3	52	F	OA	114.8	22.0	4/2	Yes	Cefazolin	< 0.3	0.3	< 0.3	48.5	16.3	6.5
4	57	M	OA	81.2	23.6	7/6	No	Vancomycin	0.3	< 0.3	< 0.3	16.3	8.9	4.1
5	72	M	OA	111.1	24.4	6/5	No	Cefazolin	< 0.3	< 0.3	< 0.3	32.4	17.8	7.0
6	64	F	OA	104.8	24.6	5/4	No	Cefazolin	< 0.3	0.3	< 0.3	14.3	23.0	13.0
7	68	M	OA	117.9	41.0	8/8	Yes	Cefazolin	0.3	< 0.3	< 0.3	25.8	12.7	4.0
8	69	F	OA	51.7	23.9	5/3	Yes	Vancomycin	< 0.3	< 0.3	< 0.3	32.5	20.1	11.9
9	69	F	OA	82.5	29.0	6/5	No	Vancomycin	0.3	< 0.3	< 0.3	59.9	19.8	9.8
10	75	F	OA	94.8	27.9	4/3	Yes	Cefazolin	0.3	0.3	< 0.3	31.2	4.2	2.2

OA = osteoarthritis; all arthroplasty components were Genesis II™ (Smith & Nephew, Memphis, TN, USA).

Table 2. Patient data for intravenous tobramycin group

Patient	Age (years)	Gender	Diagnosis	Weight (kg)	Prophylaxis	Serum 6 hours μg/mL	24 hours μg/mL	48 hours μg/mL	Intraarticular 6 hours μg/mL	24 hours μg/mL	48 hours μg/mL
1	62	M	OA	144.2	Cefazolin	1.7	1.6	2.0	2.0	2.1	2.7
2	72	F	OA	91.6	Cefazolin	0.9	0.5	0.3	1.3	0.8	1.3
3	51	M	OA	111.6	Cefazolin	1.2	4.2	3.5	1.1	1.7	1.3
4	69	F	OA	105.7	Cefazolin	1.1	5.7	0.6	1.3	1.3	1.9
5	74	M	OA	86.6	Cefazolin	5.5	0.6	3.9	1.8	1.0	1.4

OA = osteoarthritis.

placed intraoperatively. It was determined that the joint hematoma would need to be sampled for a minimum of 48 hours to adequately evaluate level kinematics, based on previous studies [3, 12]. Samples of serum and intraarticular hematomas were collected at 6, 24, and 48 hours postoperatively for tobramycin level determination. Intraarticular hematoma samples were aspirated via the Hemovac® drains using a strict sterile technique by a study physician (MK, WS). Tobramycin levels were measured using the particle-enhanced turbidimetric inhibition immunoassay (PETINIA) technique with a low-end sensitivity of 0.28 μg/mL (Dimension Vista System; Dade Behring Inc, Newark, DE, USA). Each patient was monitored for adverse reactions throughout the hospital stay and their renal function parameters were measured preoperatively and on the third postoperative day.

Aftercare and Followup

All patients enrolled in the study received additional antibiotic prophylaxis intravenously for 48 hours with either cefazolin or vancomycin until drain removal. Vancomycin was chosen for patients who had a documented penicillin allergy. All patients tolerated the tobramycin regardless of administration route, with no evidence of nephrotoxic or allergic complications. All patients were followed by their surgeon (GAV, JLP), and there were no complications or infections after one year.

Statistical Analysis

Antibiotic elution levels were measured in micrograms per milliliter (μg/mL). Mann–Whitney U tests were performed to compare the serum and intraarticular tobramycin concentrations at each time in the independent variable of group (control and tobramycin-impregnated bone cement). In addition, Spearman's correlation analyses were used to determine if component size and cement weight correlated with intraarticular tobramycin concentrations at all times. Similarly, the Mann-Whitney U test was performed to determine if the intraarticular tobramycin concentration at each time was associated with patellar resurfacing. A significance level of 0.05 was used for all statistical analyses.

Results

In the tobramycin-impregnated bone cement group, the median (interquartile range) intraarticular tobramycin concentrations at 6, 24, and 48 hours were 31.8 (29.0) μg/mL, 17.1 (13.1) μg/mL, and 6.8 (6.8) μg/mL, respectively (Fig. 1). The median (interquartile range) intraarticular tobramycin concentrations for the control group, those who were administered only intravenous tobramycin, were 1.3 (0.7) μg/mL at 6 hours, 1.3 (1.0) μg/mL at 24 hours, and 1.4 (1.0) μg/mL, at 48 hours (Fig. 2). Intraarticular tobramycin concentrations for the tobramycin-impregnated bone cement group were larger than those for the control group at 6 hours ($p = 0.002$), 24 hours ($p = 0.002$), and 48 hours ($p = 0.020$).

The serum concentrations for the tobramycin-impregnated bone cement group were 0.3 μg/mL or less for all samples and times (Fig. 2). For the control group the median (interquartile range) serum concentrations were 1.2 (2.6) μg/mL, 1.6 (4.4) μg/mL at 24 hours, and 2.0 (3.3) μg/mL at 48 hours (Fig. 2). The serum levels for the tobramycin-impregnated bone cement group were less than those for the control group at 6 hours ($p = 0.001$), 24 ($p = 0.001$), and 48 hours ($p < 0.001$).

The intraarticular tobramycin concentrations were not correlated with the cement weight at 6 hours ($p = 0.651$), 24 hours ($p = 0.556$), or 48 hours ($p = 0.751$). Similarly, intraarticular concentrations were not correlated with component size (femoral/tibial) at 6, 24, or 48 hours with p values of 0.122, 0.238, and 0.168, respectively. In addition, the intraarticular tobramycin concentration was not

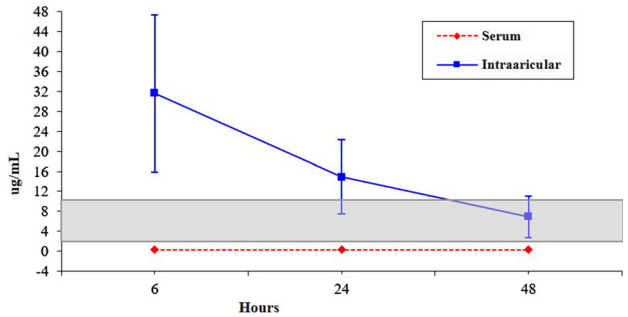

Fig. 1 For the tobramycin-impregnated bone cement group, the grey box represents the accepted serum-safe levels of tobramycin. Each time plots a single tobramycin concentration assay measurement for serum and intraarticular groups.

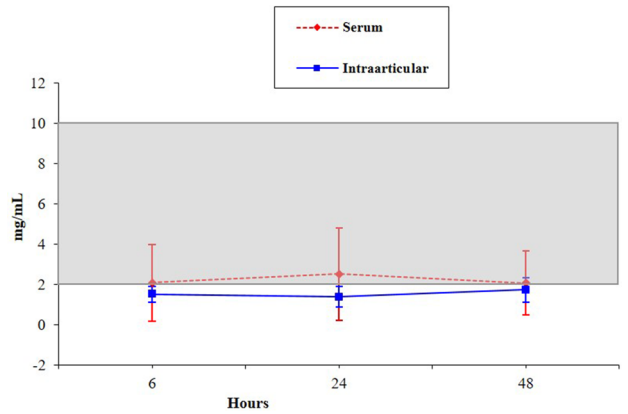

Fig. 2 For the intravenous tobramycin group, the grey box represents the accepted serum-safe levels of tobramycin. Each time plots a single tobramycin concentration assay measurement for serum and intraarticular groups.

dependent on whether the patient received patellar resurfacing at 6 hours ($p = 0.251$), 24 hours ($p = 0.917$), or 48 hours ($p = 0.754$).

Discussion

Tobramycin has been shown to be an excellent drug for addition to bone cement [10, 19, 20]. Tobramycin-impregnated bone cement has been shown to be safe, with low in vivo systemic tobramycin levels and no reported cases of allergy [3, 8, 19]. It has proven in vitro elution characteristics and is thermostable [1, 7, 15]. Low-dose tobramycin has been shown to not substantially compromise the mechanical integrity of bone cement [2]. In vivo studies have shown tobramycin-impregnated bone cement to be useful for articulating and nonarticulating spacers in treating infected arthroplasties, and for beads in treating other infected areas [1, 11, 15, 20]. Tobramycin-impregnated bone cement has been shown in vivo to produce supratherapeutic tobramycin wound hematoma levels in patients undergoing THA [3, 12, 20, 21]. These same principles and techniques are applied to TKA, although tobramycin levels achieved after implanting knee components using tobramycin-impregnated bone cement have not been reported to our knowledge, and thus provided motivation for our study. We found intraarticular tobramycin concentrations remained in the therapeutic range (> 2.0 μg/mL) 48 hours after surgery in all but one of the patients in the tobramycin-impregnated bone cement group whose final sample was subtherapeutic. In the control group, there was a subtherapeutic (< 2.0 μg/mL) level of tobramycin in all the intraarticular samples [21]. The maximum serum value obtained was 5.7 μg/mL, which was less than the usual reported threshold of 10.0 μg/mL used for intravenous administration [18]. Based on the evidence we obtained in this study, commercially prepared low-dose tobramycin bone cement achieves supratherapeutic local concentrations while maintaining minimal serum levels. Low-dose tobramycin bone cement also achieved much higher intraarticular concentrations than achieved with intravenous administration of tobramycin during the first 48 hours postoperatively. Tobramycin-impregnated bone cement had limited systemic uptake and potentially effective antibacterial activity of joint fluid during the first 48 hours after a TKA.

Limitations of our study include the use of indwelling Hemovac® drains to obtain our sample, as there was a risk of infection. The surgeons involved used the Hemovac® drains selectively in their practices during the study period, therefore this was not a deviation from typical care during that time. It was thought that the morbidity would be less than multiple joint aspirations and that sample volume would be adequate. With adequate sample volume, we were able to minimize the number of patients to enroll. In addition, this study was too small to detect uncommon complications associated with the use of tobramycin, such as toxicity or allergic reactions. For that reason, among others, our study shows efficacy, but cannot substantiate claims of safety of this treatment. Larger studies are needed for that. A final limitation is that we studied only Simplex™ P with tobramycin (Stryker Howmedica Osteonics) vacuum mixed in a bowl. Other cement products, mixing techniques, and choice of antibiotic can affect antibiotic elution [2, 3, 5, 7, 12, 15], but we used a standard product and mixing technique that was consistent between the two study surgeons.

High-dose tobramycin-impregnated bone cement used alone or in combination is well-studied and accepted for use as spacers or beads in staged revision of infected total joint arthroplasties [9–11, 13]. Low-dose tobramycin-impregnated bone cement used prophylactically for joint component implantation in high-risk patients (eg, revision

surgery, patients who are immunocompromised, staged revision for infection) also has been accepted [6, 8, 10, 20, 21]. However, routine prophylactic use of tobramycin-impregnated bone cement in all patients is controversial [6, 10, 14, 16, 17]. In a similar study with gentamycin-loaded bone cement, it was suggested that the soft tissues of the knee act as a barrier to aid in preventing the risk of toxicity from systemic diffusion of antibiotic laden bone cement [2]. Ueng et al. [23] compared antibacterial activity of joint fluid in cemented TKAs with and without antibiotic loading and found that the addition of an antibiotic-loaded cement can prolong antibacterial activity of joint fluid. Thus, our results also question the effectiveness of intravenous tobramycin as prophylaxis versus tobramycin-impregnated bone cement alone, given that our intraarticular levels were subtherapeutic for the intravenous group whereas the tobramycin-impregnated bone cement group exceeded minimal inhibitory concentrations in the joint.

The primary advantage of antibiotic-impregnated bone cement for prophylaxis is further reduction of the rate of deep periprosthetic infection. In one of the largest series of its kind, Espehaug et al. [6] looked at the Norwegian arthroplasty register and concluded that systemic antibiotics combined with antibiotic-containing bone cement led to fewer revisions than other methods. In this age of scrutinizing the cost value of prophylactic measures by healthcare systems, it has been reported that the total cost for a revision knee arthroplasty attributable to infection can range from USD 30,000 to USD 55,000 per case, whereas the additional cost of adding a packet of antibiotic cement is approximately USD 300 [16, 17]. Although our study and that of Espehaug et al. [6] support the hypothesis that antibiotic-impregnated bone cement may be used safely to reduce the incidence of infected primary total joints, prospective clinical data supporting routine prophylactic use of antibiotic bone cement in primary knee or hip arthroplasty are limited [16, 24].

Scott et al. [19] reported that prolonged continuous presence of low dosages of antibiotics increases the potential risk of microbial resistance. What is not known is the duration and antibiotic level necessary to cause this resistance. Whether it is the mechanical properties of cement that would inhibit or promote microbial biofilm adhesion or prolonged exposure to insufficient antibiotic levels that could generate genetic modifications in organisms, has not been fully be elucidated [17]. In light of this, potential disadvantages of routine use of low-dose antibiotic-impregnated bone cement can include the possible emergence of antibiotic-resistant organisms and the need for additional surgery in patients who have an allergic reaction. Further research in these issues is necessary before routine use of antibiotic-impregnated bone cement as prophylaxis could be recommended.

Based on the evidence obtained in this study, commercially prepared low-dose tobramycin bone cement can be used to obtain supratherapeutic intraarticular concentrations during the first 48 hours postoperatively while maintaining systemic levels at a minimum. Tobramycin-impregnated bone cement achieved much higher intraarticular concentrations than intravenous administration of tobramycin. Tobramycin-impregnated bone cement had limited systemic absorption and potentially effective antibacterial activity of joint fluid during the initial 48 hours after a TKA.

From the data in our study, one could make a case that prophylactic intravenous administration of antibiotics might not be warranted owing to the local concentration levels of antibiotics that can be achieved using tobramycin-impregnated bone cement in the joint during the first 48 hours postoperatively, compared with subtherapeutic joint concentrations after intravenous antibiotic administration. We wished to present our data, as it formed the basis for a followup study. Based on our results, the use of tobramycin-impregnated bone cement for cemented joint arthroplasty has been a common practice at our institution during the last 10 years. This has allowed us an opportunity to perform a long-term evaluation of the clinical effect of the routine use of prophylactic tobramycin-impregnated bone cement, which is in process.

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