

Gentamicin serum concentrations after reinfusion of blood in patients undergoing arthroplasty with gentamicin-loaded bone cement.

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Abstract:

Cement is sometimes applied to fix prostheses during arthroplasty. The cement can contain antibiotics for prophylaxis or treatment of joint infection. Gentamicin in cement is released gradually into its surroundings and can reach toxic concentrations in recovered blood. To determine gentamicin concentrations in patients with recovered blood and after blood reinfusion in patients who underwent joint replacement using gentamicin-loaded bone cement. This is a prospective observational study of 18 patients who underwent partial or total hip or knee replacement. Gentamicin-loaded bone cement was justified in all cases, and all patients were candidates for blood reinfusion after surgery. Gentamicin serum concentrations were measured by immunoassay. Serum concentrations were never higher than 1.5 µg/ml. The median concentration of gentamicin in recovered blood was 26.3 µg/ml. The maximum gentamicin dose by blood reinfusion could be 129 mg. The maximum gentamicin concentration in reinfused blood was 1.5 µg/ml. Gentamicin-loaded bone cement is safe, since drug levels did not reach toxic concentrations.

Keywords: gentamicin; arthroplasty; bone cements; blood; reinfusion.

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INTRODUCTION

Periprosthetic joint infection leads to failure of total joint replacement, with a current prevalence of 1-2%

1. Cement is sometimes applied to fix prostheses in arthroplasty owing to patient age, comorbidities, or bone quality. Implant-related infections might appear due to the formation of bacterial biofilms 2. Once the infection begins, it is challenging to treat and severely reduces patient's quality of life 3.

In order to prevent these type of infections, the cement can contain antibiotics such as gentamicin, vancomycin, or combinations for prophylaxis or treatment of joint infection 4–6. These antibiotics showed excellent eluting and material properties 2,4,7,8. In case of gentamicin, it can be combined with polymethyl methacrylate.

Liquid gentamicin is added to cement for its bactericidal properties and it is gradually released to the surrounding area. Initially, high concentrations are reached, although these diminish over time. However, local concentrations can be detected at 3 months 9. Hip and knee arthroplasties cause a significant blood loss which often requires blood transfusions to avoid perioperative anaemia 10,11. To reduce the need of allogenic transfusions, the reinfusion of filtered postoperatively collected drainage blood was settled as a proper technique 12–14. Then, blood recovery systems are increasingly used during or after surgery 15. However, as gentamicin can pass to recovered blood, it can reach detectable concentrations in systemic circulation that may cause nephrotoxicity or ototoxicity in this type of patients.

The aim of this study was to determine gentamicin concentrations in recovered blood and serum concentrations after the reinfusion in patients whose prosthesis was fixed using gentamicin-loaded bone cement.

MATERIALS & METHODS

Study design

Ours was a pilot, prospective, observational study of 18 patients (2 male and 16 female) who underwent total or partial hip or knee replacement and who were candidates for blood reinfusion after surgery.

Arthroplasty using gentamicin-loaded bone cement was justified in all cases. The bone was cemented with Palamed G® 1 x 40 (550 mg of gentamicin for each 40 g of polymethyl methacrylate). The mean values for cement weight and gentamicin concentrations were very variable. The average weight of the gentamicin-loaded bone cement was 30.98 g (range, 6 – 84.6 g).

Antibiotic prophylaxis consisted of amoxicillin-clavulanic acid or cefazolin. Patients who were allergic to beta-lactams received vancomycin. Patients with impaired renal function or gentamicin allergy were excluded.

Quantification of gentamicin

Three samples were to be drawn: the first, 2 hours after surgery; the second, from recovered blood; and the third, 30 minutes after reinfusion. Gentamicin concentrations

were determined using immunoassay (Abbott), following the procedures used in routine care laboratory, as previously described 16.

Statistical analysis

A descriptive analysis was performed to calculate mean, standard deviation, coefficient of variation, median, geometric mean and minimum and maximum of all continuous variables (age, cement weight and gentamicin concentrations). The correlation between gentamicin levels and cement weight was investigated by linear regression. P values lower than 0.05 were considered significant. The statistical analysis was performed using SPSS software v.15.0.

Ethics

The protocol complied with Spanish law on biomedical research and was approved by the Ethics Committee for Clinical Investigation of Hospital Universitario de la Princesa. Written informed consent was obtained from each patient before inclusion in the study

RESULTS

Seven patients underwent partial hip replacement surgery, 1 total hip replacement and 10 total knee re-placement. Mean age was 80.72 ± 8.68 years old. None of the patients developed nephrotoxicity or infection.

Table 1 shows gentamicin concentrations measured in serum 2 hours after surgery, in recovered blood, and in serum 30 minutes after reinfusion. However, the 3 settled samples could not be collected from the 18 patients.

The highest serum concentration 2 hours after surgery was 1.3 $\mu\text{g/ml}$ (mean of $0.56 \pm 0.43 \mu\text{g/ml}$). Gentamicin concentrations in recovered blood ranged from 1.2 to 129 $\mu\text{g/ml}$ (mean of $34.44 \pm 32.83 \mu\text{g/ml}$). Therefore, the maximum gentamicin dose would be 129 mg if the maximum volume (1 L) was reinfused.

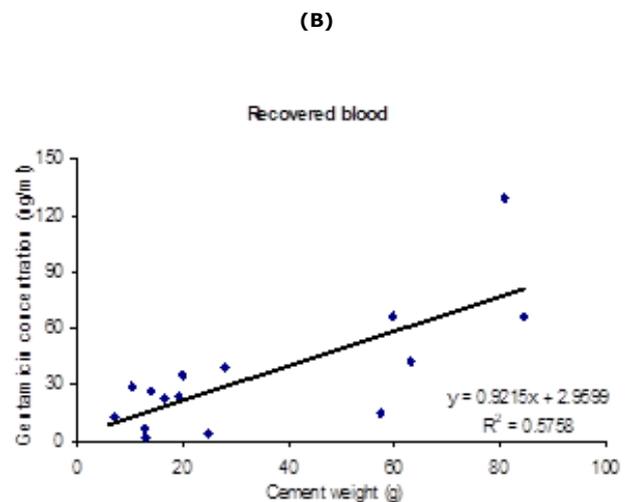
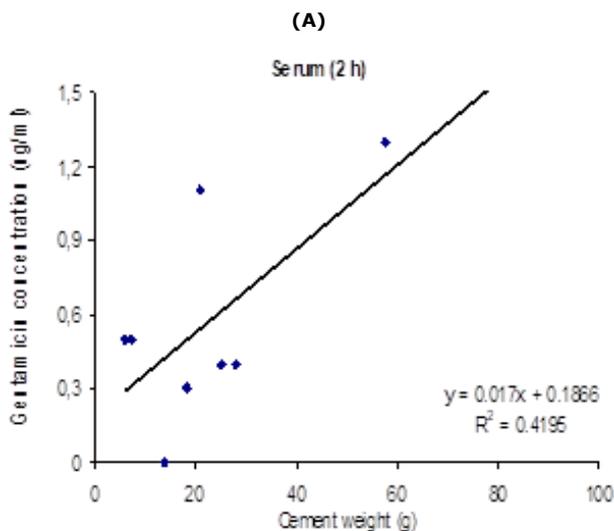
Recovered blood was finally reinfused in 5 patients. The blood volume never exceeded 1 L. The maximum serum gentamicin concentration after reinfusion was 1.5 $\mu\text{g/ml}$ (mean of $0.76 \pm 0.50 \mu\text{g/ml}$), that is, much lower than the recommended trough level ($< 2 \mu\text{g/ml}$) 17.

A correlation was observed between cement weight and gentamicin concentration (Figure 1). We observed that the greater the weight of the cement, the higher the concentration of gentamicin found in serum 2 hours after surgery, in recovered blood, and in serum 0.5 hours after reinfusion (Figure 1). We also found a correlation between gentamicin concentration in drained blood and in serum after reinfusion (Figure 2).

Table 1

Patient	Sex	Age	Joint	Cement Weight	Gentamicin concentrations (µg/ml)		
					Serum (2 h after surgery)	Recovered blood	Serum (0.5 h after infusion of recovered blood)
1	F	85	PHR	14.0	0	26.3	
2	F	72	TKR	7.2	0.5	12.6	0.5
3	M	76	TKR	6.0	0.5		
4	F	76	TKR	10.5		28.4	
5	F	89	PHR	25.0	0.4	4.1	
6	F	83	THR	28.0	0.4	38.7	
7	F	80	PHR	13.0		1.2	
8	F	84	PHR	20.0		34.8	0.6
9	F	79	TKR	16.5		22.5	0.2
10	F	80	TKR	57.5	1.3	14.6	
11	F	55	TKR	18.3	0.3		
12	F	77	TKR	84.6		66.4	
13	F	83	PHR	12.9		6.40	
14	F	86	TKR	81.0		129	
15	F	95	PHR	21.0	1.1		
16	F	92	PHR	19.2		23.5	1
26	F	78	TKR	60.0		66.2	
27	M	83	TKR	63.0		41.9	1.5
N		18		18	8	15	5
Mean		80.72		30.98	0.56	34.44	0.76
SD		8.68		25.75	0.43	32.83	0.50
CoV%		0.11		0.83	0.76	0.95	0.66
Median		81.50		19.60	0.45	26.30	0.60
GM		80.23		22.77	0	21.10	0.62
Min.		55.00		6.00	0.00	1.20	0.20
Max.		95.00		84.60	1.30	129.00	1.50

PHR: Partial hip replacement. THR: Total hip replacement. TKR: Total knee replacement. F: Female. M: Male. GM: Geometric mean. Min: Minimum. Max: Maximum.



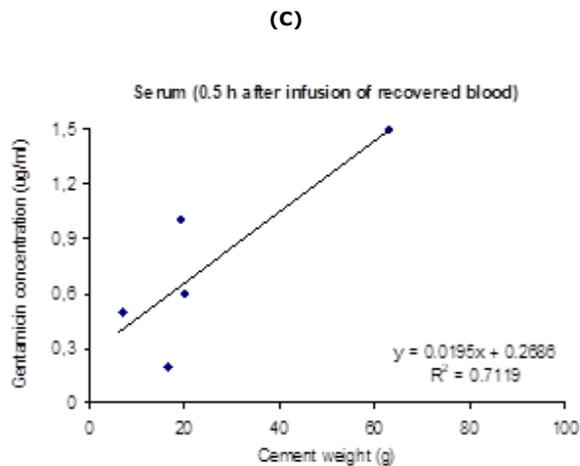


Figure 1. Correlation between cement weight in each patient and serum gentamicin concentrations 2 hours after surgery (A), gentamicin concentrations in recovered blood (B), and serum gentamicin concentrations 0.5 hours after infusion of recovered blood (C).

DISCUSSION

Arthroplasty has become a routine procedure in recent years, although postsurgical bacterial infection remains a significant complication 18. One approach to reducing the incidence of joint infection after arthroplasty involves antibiotic-impregnated bone cement to fix the implant 19. Local antibiotics provide high tissue concentrations and minimize systemic toxicity, especially nephrotoxicity. Thus, the use of antibiotic-impregnated cement lowered the infection rate by approximately 50% in primary hip arthroplasty, with no reported adverse events or complications 20. Fink et al. 21 showed that antibiotic concentrations 6 weeks after spacer implantation were sufficient to treat a periprosthetic infection.

However, little is known about the release of antibiotic from bone cement during the days immediately following surgery in humans. Release of vancomycin *in vitro* is related to the surface area of the vancomycin-loaded spacers 22: increasing the surface-to-volume ratio could enhance release.

In our study (550 mg of gentamicin in 40 g of cement), we found the mean gentamicin concentration in recovered blood to be 34.44 µg/ml. Bálint et al. 23 reported release of gentamicin from bone cement (1.48 g gentamicin in 40 g cement) in the period immediately following total hip arthroplasty. The amount of gentamicin in the wound fluid was inversely proportional to the total amount excreted. Mean gentamicin concentrations in the drain fluid diminished (2.6, 1.2, and 0.6 µg/ml, respectively at 6, 24, and 48 hours after surgery) but remained above the minimal inhibitory concentration.

We found that gentamicin concentrations were low in serum (0.56 ± 0.43 µg/ml) but high in drained blood (34.44 ± 32.83 µg/ml). A similar finding was observed in a randomised, double-blind study performed in 2 groups of 15 patients undergoing total hip replacement

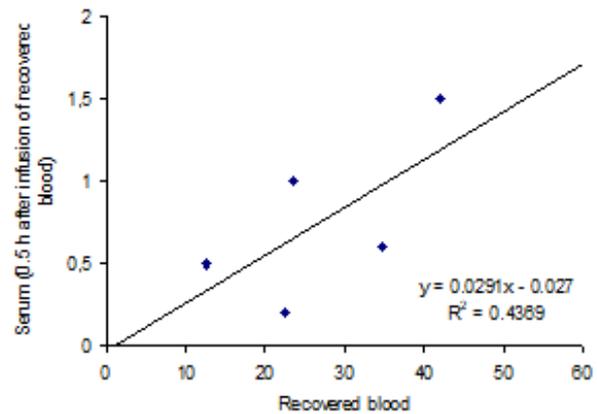


Figure 2. Correlation between gentamicin concentration in recovered blood and serum concentration 0.5 hours after infusion of recovered blood.

using antibiotic-loaded acrylic cement (0.5 g and 1.0 g gentamicin per 40 g of polymer, respectively) 24: for both gentamicin doses, the serum concentrations were low, whereas the wound drainage fluid contained highly effective antibacterial concentrations. The authors found that the highest concentration of gentamicin in serum was at 0.5 hours in both groups (1.45 µg/ml and 2.9 µg/ml, for 0.5 g and 1 g doses, respectively). In drained blood, the concentration reached 100 µg/ml for the 0.5-g dose and 308 µg/ml for the 1-g dose. The authors also found that serum, urine, and wound secretion levels showed approximately 2-fold higher concentrations in the group of patients receiving the higher gentamicin load.

Hsieh et al. 9 investigated the application of gentamicin-loaded bone cement to treat musculoskeletal infections. Forty-two patients undergoing 2-stage revision hip arthroplasty for periprosthetic infection were managed with an interim cement spacer loaded with liquid gentamicin (480 mg per 20 ml cement). Systemic antibiotic concentrations were below detectable levels in most patients, and no nephrotoxicity was detected.

The delivery of gentamicin (1.9%) and vancomycin (2.5%) from polymethyl methacrylate spacers before and after implantation for the treatment of total hip replacement infections was evaluated by Bertazzoni Minelli et al. 25. The release kinetics showed a similar pattern for both antibiotics: release was high initially, but gradually levelled off over the following months.

Anagnostakos et al. 26 also studied the release of gentamicin and vancomycin (1 g and 4 g per 80 g of cement, respectively) in drainage fluid from 28 patients. Systemic antibiotics were given postoperatively according to the antibiogram, and gentamicin and vancomycin were avoided when possible. Mean peak concentrations were reached for gentamicin and vancomycin on day 1, with no renal or hepatic dysfunction. The authors stressed the importance of additional systemic antibiotics for this procedure during the postoperative period owing to the

inferior release properties of spacers.

Regis et al. 27 studied gentamicin and vancomycin concentrations in drainage fluid obtained from patients with infected total hip arthroplasty during the first 24 hours after implantation of antibiotic-loaded polymethyl methacrylate spacers. Gentamicin and vancomycin were released from temporary hip spacers at bactericidal concentrations, whereas serum levels were below the limit of detection.

None of the patients in our study developed adverse events, although other research groups described several. Though nephrotoxicity is uncommon, there have been some reports of acute renal failure after surgery involving antibiotic-impregnated cement in infected total knee and hip arthroplasty 28–31.

Finally, our study is limited by the small sample size, since only 5 patients were reinfused. However, considering this as an exploratory study, our data show the correlation between cement weight and gentamicin concentrations, which is important to take into account for further approaches. However, even in heavier cement prosthesis, gentamicin did not reach toxic levels. Thus, our data indicate that gentamicin-loaded bone cement is safe in patients undergoing arthroplasty, even in those receiving reinfused blood.

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