Letter to the Editor

Acute Kidney Injury (AKI) with the Use of Antibiotic-impregnated Bone Cement in Primary Total Knee Arthroplasty

Dear Editor,

Antibiotic-impregnated bone cement has been used routinely in total hip and knee replacements as it has been shown to reduce the incidence of deep wound infection.[1-7] The antibiotics used include nephrotoxic gentamicin as well as tobramycin and polymyxin, besides other less nephrotoxic such as cefuroxime. The risk of nephrotoxicity from the use of the former has been deemed to be low, as while high local concentrations of the drug are produced in the vicinity of the implants, serum concentrations are kept at safe low levels.[8-10] There have been previous reports of acute kidney injury with use of nephrotoxic antibiotic-impregnated cement in large amounts as spacers, after removal of implants in infected total hip and knee replacements.[11-14] We report a patient who developed acute kidney injury (AKI) after primary total knee replacement using gentamicin-impregnated bone cement.

Case Report

A 68-year-old female with a background history of diabetes mellitus, hypertension, ischaemic heart disease, chronic hepatitis B and mild renal impairment was admitted electively for a right total knee replacement. Her baseline eGFR was 42 mL/min (normal: >60 mL/min), serum creatinine 116 μmol/L (normal: 50 to 90 μmol/L) and serum urea 9 mmol/L (normal: 2.0 to 6.5 mmol/L). Her preoperative sodium and potassium levels were 139 mmol/L (normal: 135 to 150 mmol/L) and 5.3 mmol/L (normal: 3.5 to 5.0 mmol/L) respectively. She had normal urine output preoperatively. One tablet of Nife-ten (Atenolol 50 mg and Nifedipine 20 mg) was served in the morning prior to the surgery; 1 g of intravenous cefazolin was given 1 hour before surgery and 40.8 g of Palacos R+G (Heraeus, Wehrheim, Germany) bone cement containing 0.5 g of gentamicin was used on the femoral and tibial components. Surgery was carried out under general anaesthesia and sevoflurane was used as the induction agent. Duration of surgery was 90 minutes and there were no intraoperative complications. Blood pressure and cardiac functions were normal throughout the procedure. Postoperatively, the blood pressure and pulse rate were normal and maintained at the patient's baseline levels. On postoperative day (POD) 1, the patient developed severe bradycardia with a heart rate of 52 beats per minute, and hypotension (blood pressure was 80/43 mmHg). This lasted for approximately 10 to 11 hours. Blood pressure and heart rate eventually improved after 0.6 mg of atropine was given. Estimated blood loss was not charted but postoperatively the redivac drain drained 410 mL of haemoserous fluid within the first 24 hours. Postoperative haemoglobin on POD 1 was 10.2 g/dL, from a preoperative level of 11.5 g/dL (normal 12.9 to 17.0 g/dL). An acute coronary screen returned normal. Laboratory investigations showed that the patient's creatinine was elevated at 292 μmol/L (normal: 50 to 90 μmol/L) and serum urea level was 15.4 mmol/L (normal: 2.0 to 6.5 mmol/L). Her potassium and sodium levels were 8.0 mmol/L (normal: 3.5 to 5.0 mmol/L) and 136 mmol/L (normal: 135 to 150 mmol/L) respectively. Her urine output diminished to less than 10 mL per hour. Cardiologist confirmed that the bradycardia and hypotension were due to hyperkalaemia as the electrocardiogram did not show any ischaemic changes and cardiac enzymes were normal. Acute on chronic kidney injury with severe hyperkalaemia and metabolic acidosis was diagnosed. Later in the day, her serum creatinine climbed to 330 μmol/L (normal: 50 to 90 μmol/L) and serum urea to 15.5 mmol/L (normal: 2.0 to 6.5 mmol/L). A renal physician was consulted and haemodialysis was initiated. She underwent 1 session of haemodialysis. Her creatinine level normalised to near baseline level of 138 μmol/L (normal: 50 to 90 μmol/L) by the fourth POD. Her urine output improved to 50 to 70 mL per hour. On POD 7, her renal function returned to normal. An ultrasound scan of the kidneys showed no structural abnormalities. No nephrotoxic medications such as non-steroidal anti-inflammatory drugs (NSAIDS) were given perioperatively. The patient was then discharged from hospital, well, on POD 9. Her recovery progressed uneventfully from then on, with complete wound healing and return to all her normal activities.

Discussion

Deep infection following total joint arthroplasty is a catastrophic complication both to the patient and the surgeon. The use of antibiotic-impregnated bone cement in primary knee arthroplasty is a common practice to prevent infection but a controversial one.[7,15-20] Chiu et al[2] found no deep infection in 178 knees that had been implanted with cefuroxime loaded cement, while 5 out of 162 (3.1%)

developed infection when plain cement was used. In another study,[3] the same group found no deep infection in 41 diabetic patients treated with cefuroxime loaded cement, but 5 out of 37 (13.5%) in diabetic patients where plain cement was used. Yet others have shown that antibiotic loaded bone cement did not appear to reduce primary total knee arthroplasty infection rates even in diabetic patients in a study using a community-based total joint registry.[21] Therefore, there is a need to balance the benefits with the disadvantages associated with the routine used of antibiotic-impregnated bone cement.

One of the concerns besides others[17-20] regarding antibiotic-loaded bone cement is potential nephrotoxicity if high serum levels of the antibiotic are reached. There are many pharmacokinetic studies comparing serum concentrations of the antibiotic following total joint arthroplasty using antibiotic-loaded bone cement with concentrations of the antibiotic reached in the local tissues. One such study[8] investigated 10 patients following primary total hip replacement where vancomycin-loaded bone cement (2 g of antibiotic per 40 g of cement) was used. Serum concentration was less than 3 mg/mL, which is 30 times lower than the toxic threshold, and vancomycin was not detectable in the urine after the tenth day.[8] Sterling et al[9] studied the pharmacokinetics of simplex-tobramycin bone cement (Howmedica, Limerick, Ireland) when used in total hip replacements. They collected specimens of blood, urine, and drainage fluid for 72 hours postoperatively. High concentrations of tobramycin were found in the drainage fluid, with a mean level of 103 μg/mL at 1 hour, which declined to 15.1 μg/mL at 48 hours. The mean serum tobramycin level peaked at 3 hours (0.94 μg/mL) and declined to 0.2 μg/mL by 48 hours. The mean urinary tobramycin level peaked at 12 hours (57.8 μg/mL) with a decline to 12.6 μg/mL by 24 hours. Wahlig et al[22] using gentamicin-loaded bone cement in total hip replacements showed wound drainage fluid containing highly effective antibacterial concentrations while serum and urine concentrations were low. These data suggest that the use of antibiotic-loaded bone cement at the prescribed dosages is safe and an effective method of antibiotic delivery.

There are a few previous reports of acute kidney injury with the use of antibiotic-impregnated bone cement in revision hip and knee arthroplasty where the amount of bone cement used is considerably greater than the amount used in primary arthroplasty.[10-14] In the former, large amounts of cement impregnated with antibiotics are used as spacers after removal of infected implants as a first stage of a 2-stage revision exercise. Curtis et al[11] reported a case of an 85-year-old man with a history of renal insufficiency who experienced acute kidney injury after undergoing a revision treatment of an infected knee arthroplasty. Tobramycin impregnated bone cement was used as a block spacer as the first stage after the infected implants were removed. They found nephrotoxic levels of tobramycin (2 μg/mL) in the serum even after 21 days following surgery. Explantation of the spacer and multiple sessions of haemodialysis finally returned his renal functions to preoperative levels. Dovas et al[12] also reported acute kidney injury with use of a temporary gentamicin plus vancomycin cement spacers in a 61-year-old with an infected total knee replacement. Although serum antibiotic levels were not measured, they attributed the kidney injury to high antibiotic levels in the blood as no other causes could be found. Van Raaij et al[13] also reported acute kidney injury following use of gentamicin-impregnated cement spacers for an infected total knee replacement and found toxic levels of the antibiotic in the serum. Patrick et al[14] reported the same complication with a vancomycin and tobramycin laden cement spacer after removal of an infected total hip replacement. All authors attributed elevated levels of the nephrotoxic antibiotics in the serum for the kidney injury. Wahlig et al[22] have shown that the amount of antibiotic in the serum would increase proportionate to the amount in the cement and the amount of cement used. The amount of cement used as spacers would be much more than when used to line implants in the primary joint replacements. AKI in these patients could be explained by the highly toxic levels of the antibiotics that could be reached in the serum.

To our knowledge, there is no previous report of AKI with the use of antibiotic-impregnated bone cement in primary knee arthroplasty. Serum levels of the antibiotics are known to be at safe levels with the use of antibiotic-loaded cement in this situation, although the levels were not measured in our patient. Mild renal impairment may have led to poor excretion of the drug resulting in a rise to toxic levels. We were not able to obtain a serum gentamicin level due to the rapid progression of events leading to the development of AKI at the time in question. Using the Naranjo probability scale,[23] we deemed that the use of gentamicin in the cement to be the probable cause of the patient's AKI (score: 6 out of 10) (Table 1). Our patient recovered her renal function after 1 session of haemodialysis.

We postulate that the pre-existing renal impairment may have impaired the excretion of the antibiotic resulting in a rise to toxic levels. Sterling et al[9] also reported a renal impaired patient whose serum creatinine rose from 0.15 mmol/L preoperatively to 0.21 mmol/L, 48 hours following a primary total hip replacement using tobramycin laden cement. Her serum tobramycin rose to toxic levels of 2.1 μg/mL at 12 hours post surgery. Unlike our patient, their patient did not require haemodialysis and renal functions returned to normal by day 5. Routine use of the antibiotic laden cement in joint replacements has been associated with

Table 1. The Naranjo Adverse Drug Reaction (ADR) Probability Scale*

Questions	Yes	No	Do not know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	+1
2. Did the adverse event occur after the suspected drug was administered?	+2	-1	0	+2
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	0
4. Did the adverse reaction reappear when the drug was readministered?	+2	-1	0	0
5. Are there alternative causes (other than the drug) that could have on their own caused the reaction?	-1	+2	0	+2
6. Did the reaction reappear when a placebo was given?	-1	+1	0	0
7. Was the blood detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	+1
			Total	+6

*the ADR is assigned to a probability category from the total score as follows: 'definite' if the overall score is 9 or greater, 'probable' for a score of 5 to 8, 'possible' for 1 to 4 and 'doubtful' if the score is 0

other potential disadvantages besides nephrotoxicity. These include impaired mechanical strength of the cement, allergic reactions, antimicrobial resistance and increased costs.[7] Perhaps antibiotic laden cement should only be indicated in high-risk patients with insulin dependent diabetes, haemophilia, malignancy, malnourishment, inflammatory arthritis or previous joint infection.[7]

Although no clear guidelines can be given, our case report and that by Sterling et al[9] point to risks patients with pre-existing renal impairment face when nephrotoxic antibiotic laden cement is used during joint replacement surgery. Vigilance may also be required in the elderly, diabetic or hypertensive patients with apparently normal renal function who may have subclinical renal impairment.

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