

# A retrospective study of acute kidney injury in hip arthroplasty patients receiving gentamicin and dicloxacillin

Sandra JOHANSSON, Ole M CHRISTENSEN, and Anders H THORSMARK

Department of Orthopedics and Traumatology, Holbaek Hospital, Holbaek, Denmark  
Correspondence: san\_johans@hotmail.com  
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**Background and purpose** — Acute kidney injury is a known complication of antibiotic use. Antibiotic prophylaxis is essential to prevent periprosthetic infections after total hip replacement. We experienced a rise in the incidence of acute kidney injury (AKI), and in an effort to solve this problem, we changed our antibiotic prophylaxis protocol. We investigated whether removing gentamicin from our antibiotic protocol would cause fewer and less severe cases of renal impairment.

**Patients and methods** — We performed a retrospective study involving 136 cases of total hip replacement, with 66 patients receiving dicloxacillin and gentamicin and 70 patients receiving dicloxacillin alone.

**Results** — We found less cases of AKI in the dicloxacillin group ( $p = 0.03$ ): the mean creatine level in the dicloxacillin/gentamicin group was 126 (25–422)  $\mu\text{mol/L}$  whereas it was 93 (39–278)  $\mu\text{mol/L}$  in the group that received dicloxacillin alone. We also found that cases were less severe in the dicloxacillin group than in the dicloxacillin/gentamicin group ( $p = 0.02$ ). The relative risk of developing AKI was 3 times higher if dicloxacillin and gentamicin were both used ( $p = 0.02$ ).

**Interpretation** — After removing gentamicin, there were fewer and less severe cases of acute kidney injury

prophylactic regime was suspected of giving a high risk of kidney injury due to the known nephrotoxicity of gentamicin (Quiros et al. 2011, Wargo and Edwards 2014). It is unknown whether exclusion of gentamicin from the antibiotic regime causes noticeable changes in the severity and number of cases of acute kidney injury (AKI).

In our department, we noticed a dramatic rise in the number of elective total hip arthroplasty (THA) patients who showed clinical and biochemical symptoms of kidney damage in the years 2010–2013. This rise in cases coincided with the introduction of dicloxacillin/gentamicin prophylaxis. Gentamicin was suspected of being the main cause of this rise, and it was therefore removed from our antibiotic protocol. We investigated whether dicloxacillin alone was associated with fewer and less severe cases of AKI after elective THA compared to dicloxacillin and gentamicin together.

## Methods

We performed a retrospective study involving 136 patients who underwent elective cemented (non-antibiotic-loaded cement) or uncemented total hip replacement. All the patients were treated according to current local guidelines. A list of all patients who underwent THA surgery during that period was retrieved. Using the medical records, we documented the dosage and type of antibiotics used and collected numerical data on pre- and postoperative creatinine levels during the hospital stay. The preoperative creatinine level was measured less than 2 months before the surgery in all cases. The postoperative creatinine level was measured for the first time during the first or second day after surgery in all patients. Acute kidney injury was graded using the classification developed by KDIGO (2012), in which AKI is graded in 3 stages (Table 1).

It is accepted standard that patients undergoing hip joint replacement should receive prophylactic antibiotics to prevent postoperative infections. The type and dose of antibiotics varies between countries, and in Denmark even between hospitals. Cefuroxime has traditionally been the first choice. When cefuroxime and other broad-spectrum antibiotics became associated with *Clostridium difficile*-associated disease (CDAD) (Baxter et al. 2008), guidelines were changed and gentamicin with dicloxacillin was introduced as the standard prophylaxis in many Danish hospitals. However, this new

Table 1. KDIGO classification of acute kidney injury (AKI)

AKI staging	Serum creatinine
Stage 1	Increase to 150–200% from baseline or increase of $\geq 26.5 \mu\text{mol/L}$ (0.3 mg/dL).
Stage 2	Increase to 200–300% from baseline.
Stage 3	Increase to more than 300% from baseline or increase of $\geq 354 \mu\text{mol/L}$ (4.0 mg/dL) with an acute increase of $\geq 44 \mu\text{mol/L}$ (0.5 mg/dL)

Table 2. Characteristics of the 2 groups

	Dicloxacillin/ gentamicin	Dicloxacillin	p-value
No. of patients	66	70	–
Sex (men/women)	29/37	28/42	0.6
Mean age, men (SD)	69 (2.2)	70 (1.7)	0.8
Mean age, women (SD)	72 (1.6)	71 (1.7)	0.6
Mean dicloxacillin dose (SD), g	4.92 (1.13)	4.49 (0.85)	0.01
Mean gentamicin dose (SD), mg	174 (58)	–	–
Creatinine level <sup>a</sup> (SD)			
mean preoperative	79 (27)	77 (21)	0.6
maximum	126 (83)	93 (46)	0.04

<sup>a</sup>  $\mu\text{mol/L}$

## Statistics

The patients were divided into 2 groups, with or without gentamicin, and renal injury status was classified according to KDIGO. The Wilcoxon-White rank-sum test was performed for differences between the 2 study groups, as this was a retrospective study. For differences in treatment regimen, 2-tailed chi-square analysis for significance was performed. An exact 2-tailed Wilcoxon-White rank-sum test was performed for differences in severity between the 2 treatment regimens. A regression analysis was done for relative risk of developing AKI, with the variables sex and age per decade. The level of significance was set at  $p < 0.05$ . Statistical analysis was performed using STATA software version 13.1.

## Results

We included 136 patients who underwent elective total hip arthroplasty during the period 2010–2014: 57 male patients with a median age of 69 (45–88) years and 79 female patients with a median age of 71 (42–88) years. Sex distribution and preoperative creatinine levels were similar between the 2 groups (Table 2).

The first group (74 patients) received dicloxacillin and gentamicin; they were operated on during the period October 10, 2010 to August 31, 2011. 8 patients were excluded because they had received other types of antibiotics or because we lacked information on pre- or postoperative creatinine levels.

Table 3. No. of patients who developed AKI

AKI staging	Dicloxacillin/gentamicin	Dicloxacillin
Stage 1	3	5
Stage 2	7	3
Stage 3	8	1
No AKI	48	61
Total no. of patients	66	70

The 66 patients who were included received prophylaxis consisting of 2–9 g intravenous dicloxacillin and 120–240 mg intravenous gentamicin. The mean dicloxacillin dose was 4,924 mg and the mean gentamicin dose was 174 mg.

The second group (79 patients) received dicloxacillin alone; they were operated on during the period August 7, 2014 to October 20, 2014. 9 patients were excluded because they had received other types of antibiotics. The 70 patients who were included received 1–6 g of dicloxacillin intravenously. The mean dicloxacillin dose was 4,485 mg. This group therefore received slightly lower amounts of dicloxacillin than the other group (Table 2). The local guidelines recommend 2 g perioperatively and 1 g  $\times$  3 during the first 24 hours postoperatively.

The dicloxacillin/gentamicin group had a mean preoperative serum creatinine level of 79 (36–227)  $\mu\text{mol/L}$ . The maximum serum creatinine level was 126 (25–422)  $\mu\text{mol/L}$ . There were 48 patients with no AKI, 3 with AKI of stage 1, 7 with stage 2, and 8 with stage 3.

The dicloxacillin-only group had a mean preoperative serum creatinine level of 77 (38–278)  $\mu\text{mol/L}$  and a maximum serum creatinine level of 93 (39–278)  $\mu\text{mol/L}$ . There were 61 patients with no AKI, 5 with AKI of stage 1, 3 with stage 2 and 1 with stage 3 (Table 3). In the dicloxacillin group, the creatinine level of 1 of the patients who developed AKI (stage 1) had returned to normal when measured 2 days later. The rest of the patients who developed AKI had elevated serum creatinine levels for more than 24 hours.

Overall, the dicloxacillin-only group had less severe cases of AKI ( $p = 0.02$ ). The overall odds ratio (OR) for developing AKI was 3.2 in the dicloxacillin/gentamicin group (95% CI: 1.2–8.5;  $p = 0.02$ ). Male sex had a lower OR of 0.49 (95% CI: 0.19–1.23;  $p = 0.01$ ). Age group per decade showed no statistically significant additional risk.

## Discussion

We confirmed that prophylaxis with dicloxacillin alone was associated with fewer cases of AKI and also with less severe cases of AKI. The risk of developing AKI was 3 times higher in the dicloxacillin/gentamicin group.

According to the Danish Hip Arthroplasty Register, the current rate of THA for arthrosis is 160 per 100,000 inhabitants.

This number can be expected to grow in the future as a result of changing demographics. Acute kidney injury is a known but not extensively studied complication of hip replacement surgery (Pulido et al. 2008). Perregaard et al. (2016) found that 2.2% of elective hip replacement patients developed AKI postoperatively. There have been a number of studies showing that antibiotic prophylaxis consisting of gentamicin and flucloxacillin is associated with a higher rate of AKI than prophylaxis with cephalosporins (Craxford et al. 2014, Bailey et al. 2014, Bell et al. 2014). We performed a retrospective study in an effort to investigate the frequency of AKI after removing gentamicin from our antibiotic prophylactic regime of dicloxacillin and gentamicin. With a fair number of patients, we were able to confirm our clinical hypothesis—that the incidence, severity, and relative risk of AKI was lower after we had removed gentamicin from the prophylactic regime. The group with the lower incidence of AKI also received slightly lower doses of dicloxacillin, which may have contributed to decreasing the risk of developing AKI, as shown by Challagundla et al. (2013). The reason for using a lower dose of dicloxacillin in this group was probably that the orthopedics department became more aware of the problem with antibiotics and AKI.

Previous studies have shown that hypovolemia, hypotension, and NSAIDs are among the risk factors for development of AKI (Kateros et al. 2012, Craxford et al. 2014). We are aware that our study did not take account of information about other medications, perioperative bleeding, peri- and postoperative fluid administration, or comorbidity—including previous kidney disease. Another limitation of the study was the limited number of patients with previous chronic kidney disease. Only 8 patients in each group had elevated serum creatinine levels preoperatively. This is most probably a result of selection bias, as surgeons would be reluctant to refer patients with previous kidney disease for an operation. Patients with moderate-to-severe chronic kidney disease appear to have a higher risk of developing AKI (Perregaard et al. 2016). The patients were drawn from the same population and were operated by the same surgeons, and there was no difference in comorbidity index seen in the Danish Hip Arthroplasty Register, but despite this we cannot be certain that there were no significant differences between the groups regarding these factors.

Our department has continued to use dicloxacillin alone as prophylaxis for THA patients, with special care not to exceed the recommended antibiotic regime. As before, we use non-antibiotic-loaded cement. All the postoperative infections

have been registered according to Danish regulations. No rise in acute infections has been seen since the change in antibiotic regime. It is not yet possible to make any conclusions about late infections.

In conclusion, we found fewer and less severe cases of acute renal injury after we excluded gentamicin from the THA prophylactic regime and became more cautious with the use of dicloxacillin. We recommend that other departments should investigate their prophylactic antibiotic regimens if a rise in acute kidney injury is seen.

SJ: data collection, main writer. OMC: statistical analysis, co-writer. AHT: data collection, statistical analysis, co-writer.

No competing interests declared.

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