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The Surgeon, Journal of the Royal Colleges of Surgeons of Edinburgh and Ireland

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Changing antibiotic prophylaxis for primary joint arthroplasty affects postoperative complication rates and bacterial spectrum

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ARTICLE INFO

Article history:
Received 21 January 2012
Received in revised form
24 February 2012
Accepted 26 February 2012
Available online 17 June 2012

Keywords:
Antibiotic prophylaxis
Bacterial spectrum
Clostridium difficile associated diarrhoea (CDAD)

ABSTRACT

Background: The reduction of *Clostridium difficile* associated diarrhoea (CDAD) is a national priority. As part of the *C. difficile* improvement plan in our Trust, antibiotic prophylaxis for primary arthroplasty was changed from cefuroxime to gentamicin. Gentamicin was chosen following a review of the sensitivity profiles of all the organisms isolated from infected primary arthoplasties.

Methods: From January 2002 to September 2007, 6094 patients (Group 1) undergoing primary hip and knee arthroplasty received three doses of Cefuroxime as prophylaxis; while from October 2007 to February 2009, 2101 patients (Group 2) received single dose Gentamicin (4.5 mg/kg). We studied the rate of CDAD as well as several other postoperative complications, including rate of return to theatre (RTT), before and after the change.

Findings: There was an insignificant fall in CDAD from 0.18% to 0% ($p = 0.08$) in Group 2, however there was a statistically significant increase in pneumonia (0.67–1.33%, $p < 0.01$), acute renal failure (ARF) requiring HDU admission (0.07–0.33%, $p < 0.01$) and RTT (1.08–1.95%, $p < 0.01$) in this group. RTT for proven infection increased from 0.66% to 1.52% ($p < 0.01$).

Conclusions: We conclude that Gentamicin 4.5 mg/kg alone should not be used as prophylaxis for primary joint arthroplasty as it does not reduce CDAD significantly but increases the risk of other postoperative complications. We have changed our prophylaxis to low dose gentamicin (3 mg/kg) combined with Teicoplanin 400 mg given once.

Introduction

Antibiotic prophylaxis has been demonstrated to reduce the incidence of wound infection after joint arthroplasty.[1] It is recommended by the National Institute for Health and Clinical Excellence (NICE),[2] the British Orthopaedic Association (BOA),[3] and by the National Surgical Infection Prevention Project in the United States.[4] A systematic review carried out in 2008 showed that antibiotic prophylaxis reduces the relative risk of wound infection by approximately eighty percent compared with no prophylaxis.[1] A survey of BOA members carried out in 2009 found that the hospital trusts of 88% respondents provided a protocol for the use of prophylactic antibiotics and that 58% used cefuroxime, which is in keeping

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1479-666X/$ – see front matter
doi:10.1016/j.surge.2012.02.007

with Scottish Intercollegiate Guideline Network guidelines recommending multiple dosing over 24 h.[5]

Cephalosporins alter the normal gut flora and are one of the most frequently implicated group of antibiotics in the development of *C. difficile* associated diarrhoea (CDAD).[6] Voluntary reporting of 55,000 cases of CDAD in 2006 in England prompted Health Protection Agency (HPA) and Chief Medical Officer guidance and targets.[7] Cephalosporin prophylaxis in joint replacement was identified as a potential contributor to the development of CDAD.

In 2007–2008, a Trust-wide *C. difficile* improvement plan was launched. This included a revision of the hospital antibiotic guidelines (July 2007), introduction of chlorine-containing cleaning agents in patient areas (August 2007),[8] root cause analysis, education and audit programmes, proton pump inhibitor guidelines, commencement of 'Deep Clean' (January 2008)[9] and hydrogen peroxide fumigation (June 2008). In October 2007 antibiotic prophylaxis for joint replacement was changed from Cefuroxime to Gentamicin Trust-wide. Gentamicin was chosen following a review of the sensitivity profiles of all the organisms isolated from infected primary arthoplasties. We have studied the impact of this change on CDAD, and on other postoperative complications including wound infection, pneumonia, urinary tract infection (UTI) and acute renal failure (ARF). In addition we have examined the microbiological spectrum and antibiotic sensitivities of organisms isolated from any postoperative wound infections.

Materials and methods

All patients undergoing primary total hip and knee replacement between January 2002 and February 2009 at three participating district hospitals were included in the study. Group 1 comprised patients operated on between 1 May 2002 and 30 September 2007; these all received three doses of intravenous Cefuroxime 750 mg as prophylaxis (one at induction and two postoperatively, over 24 h). All patients operated on between 1 October 2007 and 26 February 2009 received a single dose of Gentamicin 4.5 mg/kg at induction (Group 2). The dose was based on ideal body weight to ensure optimal dosing of obese or underweight patients. Gentamicin-loaded cement (0.5 g per 40 g mix) was used in both groups.[10]

Hospital episode statistics collected by all healthcare providers in the UK (including independent hospitals) on NHS patients, describe each patient episode in terms of medical diagnosis and complication codes.[11,12] Individual episode data is linked to complications which result in re-admission after a successful discharge is included. By employing the appropriate codes, complication rates following primary joint arthroplasty can be identified. (Table 1) Data was requested with regard to the incidence of CDAD, UTI and pneumonia (as defined by the HPA)[13] within 30 days of surgery. Data was collected on all patients who returned to theatre (RTT) after their primary arthroplasty up to 1 year. The medical records of these RTT patients were scrutinised to determine whether the procedure was related to their joint replacement. The microbiological records of those patients were also examined to determine if samples had been taken at the time of surgery. If the microbiological and clinical findings fulfilled the HPA definition criteria,[14] this was recorded as RTT.

The infecting organism and sensitivity profile were recorded. Sensitivity testing was performed manually (a combination of Stokes and BSAC methods) until May 2007, after which the system was automated using the VITEK 2 system (bioMérieux®, Maray l'Etoile, France). The incidence of ARF was also recorded, however as a relatively small deterioration in renal function was triggering a diagnosis of ARF, only the patients who were diagnosed with ARF requiring admission to the high dependency unit (HDU) were included in our study. Gentamicin commonly causes a temporary rise in creatinine and so those patients whose renal function quickly recovered, not requiring HDU admission were not included in the figures. Admission to HDU/ITU per se was not an endpoint in this study. Data was analysed using Fishers exact test, and a p value of less than 0.05 was considered as statistically significant.

Results

A total of 6094 patients were included in Group 1, while Group 2 comprised 2101 patients. The two groups were matched for patient age and for proportion of hip and knee procedures. More operations were performed per month in Group 2 (123 operations per month compared to 75 in Group 1, Table 2). This reflects the increased volume of work that the Trust agreed to perform in this period, due to service reorganization and expansion, and the implementation of a fast-track programme.[15] Of note there was a statistically significant increase in pneumonia (0.67% vs. 1.33%, $p < 0.01$) and acute renal failure requiring HDU admission (0.07% vs. 0.33%, $p < 0.01$). There was a reduction in CDAD from 0.18% to 0%, which was not statistically significant ($p = 0.08$). Finally the rate of RTT increased significantly, for all reasons (from 1.08% to 1.95%, $p < 0.01$) and for infection alone (from 0.66% to 1.52%, $p < 0.01$). These trends are depicted in Fig. 1.

Figure 2 depicts the spectra of organisms causing prosthetic joint infection in the two groups. There was no significant difference in the microbiological profile of infecting organisms between the two groups. There were statistically insignificant trends towards a higher proportion of *Methicillin-sensitive Staphylococcus aureus* (MSSA) and *streptococcus sp.*, and lower proportions of *Methicillin-resistant Staphylococcus aureus* (MRSA) and *Enterococcus* sp. in Group 2. Although there were no significant changes in the bacterial spectrum of infecting organisms, there were trends towards changing antibiotic resistance, especially an increasing resistance to Gentamicin amongst the *Coagulase negative Staphylococci* (CNS).

Discussion

Antibiotic prophylaxis is proven to reduce wound infection after joint arthroplasty. It has been estimated that one infection is prevented for every 13 patients receiving prophylaxis. The cost of infection after joint replacement has been estimated to be between $50,000 and $100,000 (£ 32,000–64,000).[16,17] Several trials comparing prophylactic

Table 1 – International statistical classification of diseases and related health problems [10th revision], ICD-10 codes, and surgical procedure (Office of Population, Censuses and Surveys Classification of Surgical Operations and Procedures [4th revision], OPCS-4 codes).

Elective procedure	Complication within 30 days	Return to theatre within 30 days
TKR:	A047 *C. difficile*	W80.1–3, W80.8–9
W40.1 Cemented	N17 Renal failure	Open debridement and irrigation of joint
W41.1 Uncemented	J18, J22 plus Y83	W81 Other open operations on joint
W42.1 Unspecified	Pneumonia	W90 Puncture of joint
THR:	N390 Urinary tract infection	W92 Other operations on joint
W37.1 Cemented		S47.2 Drainage of lesion of skin
W38.1 Uncemented		Specifically for TKRs:
W39.1 Unspecified		W87 Diagnostic endoscopic examination of knee joint
W93.1 Hybrid, cemented acetabular component		W42.4 Attention to total prosthetic replacement of knee joint NEC with Y221
W94.1 Hybrid, cemented femoral component		Specifically for THRs:
W95.1 Hybrid, unspecified		W39.4 Attention to total prosthetic replacement of hip joint NEC with Y221

Cephalosporins to no antibiotics have demonstrated a significantly reduced infection rate in arthroplasty surgery.[18–21] Evidence supporting systemic Gentamicin as routine prophylaxis is not well published. However the benefit of Gentamicin-impregnated cement combined with systemic antibiotics is well documented.[22–25] Antibiotic-impregnated cement has been shown in a meta-analysis to reduce infection rate by approximately 50% in primary arthroplasty.[26] The incidence of CDAD in orthopaedic patients has not been well established and will be strongly influenced by unique local factors. Kurd et al identified a rate of 0.16% in 9880 primary and revision arthroplasty patients and concluded that CDAD was associated with ASA score, hospital duration and number of antibiotics administered. The study did not distinguish between prophylactic and treatment antibiotics.[27]

Recent work by Jeavons et al. found that changing antibiotic prophylaxis for hip fracture surgery from Cefuroxime to single dose Gentamicin and Amoxicillin, significantly reduced both the length of stay (17 vs. 13 days, $p = 0.04$) and the incidence of CDAD (6–0%, $p = 0.02$).[28] Al-Obaydi et al. also found that changing from Cefuroxime to Gentamicin and Flucloxacillin as prophylaxis for hip and knee replacement and hip fracture surgery resulted in a significant reduction in CDAD rate (3.7 vs. 1.3%, $p < 0.005$) but no change in deep wound infection rate.[29] We also found that switching from Cefuroxime to Gentamicin reduced the rate of CDAD (from 0.18% to 0%) although this was not statistically significant. It may also have been influenced by other measures introduced during this time, as part of the *C. difficile* improvement plan. Although the rate of CDAD did fall, the incidence of other postoperative complications increased. The incidence of pneumonia increased from 0.67% to 1.33% and that of ARF (requiring HDU admission) increased from 0.07% to 0.3%. Most significantly, the rate of return to theatre for infection increased from 0.66% to 1.52%. All of these results are statistically significant.

Antibiotic resistance to several antibiotics appeared to increase in Group 2. This may reflect a true increase in resistance but may also be related to a change in methods for sensitivity testing and in the use of other antibiotics for treatment of other infections. The most significant result with

Table 2 – Complication rates in the two groups.

	Group 1	Group 2	
	1 May 2002–30 Sep 2007	1 Oct 2007–28 Feb 2009	
Prophylaxis	Cefuroxime	Gentamycin	
No of patients	6094	2101	
Mean age (years) [median]	69.2 [70]	68.9 [70]	
THR: TKR	2769:3325	858:1243	
Unit 1:Unit 2: Unit 3	2752:1378:1964	924:614:563	
CDAD	11 (0.18%)	0 (0.0%)	$P = 0.08$
UTI	90 (1.48%)	28 (1.33%)	$P = 0.67$
Pneumonia	41 (0.67%)	28 (1.33%)	$P < 0.01$
ARF requiring HDU	4 (0.07%)	7 (0.33%)	$P < 0.01$
Total RTT for infection	40 (0.66%)	32 (1.52%)	$P < 0.01$

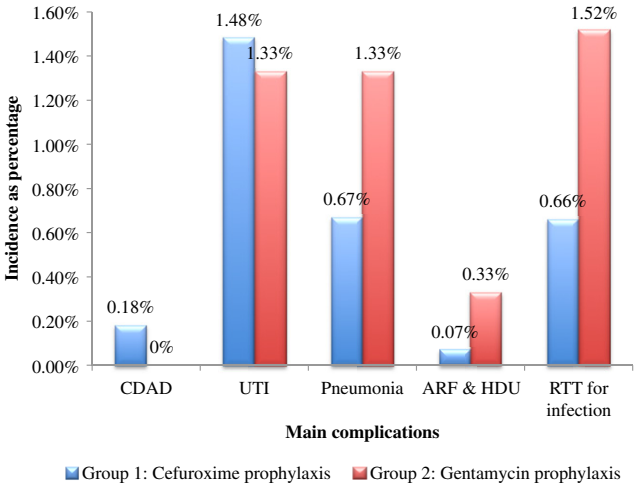

Fig. 1 – Complication rates compared between the two groups.

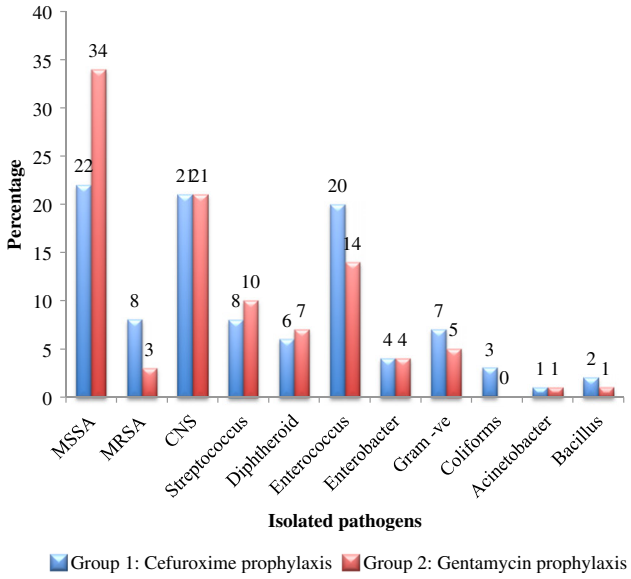

Fig. 2 – Bacterial spectrum of subsequent prosthetic joint infections compared between the two groups. MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; CNS, coagulase negative *Staphylococcus*.

regard to antibiotic resistance is probably the increase in gentamicin resistance in the coagulase negative staphylococci which has been reported to be the most common cause of infection in total hip and knee replacement.[30–32] This has influenced our current prophylaxis regime.

There are potential limitations in our study. Coding of complications requires accurate documentation in the case notes. This has been subject to a separate audit confirming that our unit has extremely accurate and robust coding mechanisms.[33] There were changes to *C. difficile* and MRSA preventative protocols during the course of the study. Access to critical care beds may have changed since the early days of this study and the increased admission to HDU for ARF may reflect easier access rather than increased severity of organ failure. Gentamicin has a different spectrum cover from cefuroxime, possibly accounting for increase in pneumonia and wound infections. Gentamicin is known to be nephrotoxic, however single dose prophylaxis was deemed safe by microbiological guidance. Nonetheless the incidence of ARF increased.

Concerned about increased wound infection and ARF identified in this study, we have changed our prophylaxis to low dose gentamicin (3 mg/kg) combined with teicoplanin 400 mg given once, to cover gentamicin resistant staphylococci (mainly the coagulase negative staphylococci) as well as improved cover for streptococci and enterococci. The rate of CDAD was reduced by changing prophylaxis, however the actual number of cases of CDAD was very small in both groups and power of this calculation was low (power = 0.49). Therefore the reduction was not statistically significant. The increases in ARF, pneumonia and RTT for infection in the group given gentamicin are statistically significant with power calculations of 0.72, 0.85 and 0.92 respectively.

Conclusions

The reduction in CDAD produced by the switch to gentamicin needs to be balanced against the increase in morbidity from increased wound infection, pneumonia and ARF. We recommend that single dose Gentamicin (4.5 mg/kg) alone is not used as prophylaxis for joint replacement.

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