Clostridium difficile in patients undergoing primary hip and knee replacement

P. J. Jenkins,
K. Teoh,
P. M. Simpson,
J. Dave,
A. H. W. R. Simpson,
S. Breusch

From Royal Infirmary, Edinburgh, United Kingdom

Antibiotic prophylaxis is routinely administered during joint replacement surgery and may predispose patients to *Clostridium difficile*-associated disease (CDAD). The primary aim of this study was to determine the incidence of this following joint replacement, using a cefuroxime-based regimen. Patients developing CDAD were compared with a control group of patients without CDAD. The incidence of the former was 1.7 per 1000 primary joint replacements. Those patients prescribed additional antibiotics had a higher incidence of CDAD (p = 0.047), but there was no difference between the two groups in relation to the use of gastroprotective agents (p = 0.703). A trial of a new prophylaxis regimen would require 43 198 patients in each arm to show a reduction of one case per 1000 procedures. Cefuroxime-based antibiotic prophylaxis is safe in patients undergoing primary elective joint replacement.

■ P. J. Jenkins, MRCS(Ed), Specialty Registrar
■ K. Teoh, BSc, MBChB, Specialty Registrar
■ P. M. Simpson, FRCSEd(Tr & Orth), Specialty Registrar
■ J. Dave, FRCPath, MD, MBA, Consultant Microbiologist
■ A. H. W. R. Simpson, DM(Oxon), FRCS, Professor of Orthopaedic Surgery
■ S. Breusch, MD, PhD, FRCSEd, Consultant Orthopaedic Surgeon
Department of Orthopaedic Surgery
Royal Infirmary of Edinburgh, Old Dalkeith Road, Edinburgh EH16 4SU, UK.

Correspondence should be sent to Mr P. J. Jenkins; e-mail: paul@jenkinsnet.org.uk

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Clostridium difficile is a Gram-positive spore-forming bacterium which causes diarrhoea. Infection ranges from asymptomatic carriage to pseudomembraneous colitis and toxic megacolon (*C. difficile*-associated disease, CDAD). Recent reports have shown a 30% increase in death due to *C. difficile* between 1984 and 2000, and an increased overall incidence of 3.5% to 15.3% over the same period.[1] Its aetiology is not fully elucidated, but it is thought to be an iatrogenic complication of antimicrobial prophylaxis or therapy,[2-8] particularly with third-generation cephalosporins, clindamycin and ciprofloxacin.[9] A recent study has shown an incidence of 0.16% in patients undergoing total joint replacement.[1] Antibiotics are universally used to prevent deep infection in total joint replacement and have been shown to reduce rates of deep infection significantly.[10] Agents are chosen depending on the most likely infectious organism and side-effect profile.[10-13] Our arthroplasty unit uses a prophylaxis regimen in common use that consists of three doses of intravenous cefuroxime (one dose at anaesthetic induction, followed by two more doses at eight-hourly intervals). This provides cover against most Gram-positive and Gram-negative bacteria that may contaminate the wound, and achieves rapid tissue concentrations. There is debate concerning the optimal prophylaxis regimen which is related to the level of risk of CDAD associated with peri-operative antibiotics and a trend to avoid cephalosporin prophylaxis.

The primary aim of this study was to determine the incidence of *C. difficile* in patients undergoing primary total joint replacement at our institution. The secondary aim was to perform a case-controlled retrospective study to examine the influence of comorbidity, complications, prescription of other additional antimicrobial agents, and the use of gastric acid suppressors on the incidence of CDAD. The final aim was to perform a power calculation using the data derived from this study, to determine the sample size necessary for future studies seeking to compare antibiotic regimens in total joint replacement.

Materials and Methods

A retrospective case-control study was performed. An infection-control administrative database was searched and 83 patients who developed CDAD in our unit between January 2006 and December 2008 were identified. This database also allowed us to detect cases of CDAD that occurred following discharge to the community or rehabilitation. Any patient who developed loose bowels had their bowel movements documented on a stool chart, and samples were sent to assay for *C. difficile* toxin and for routine enteric culture. It was assumed that any patient with persistent loose bowel movements in the community would have stool samples sent by their general practitioner.

Table I. Incidence of *Clostridium difficile*-associated disease (CDAD) following total hip and knee replacement

	Total hip replacement				Total knee replacement				Overall joint replacements			
	CDAD	Total	Incidence		CDAD	Total	Incidence		CDAD	Total	Incidence	
Year	(n)	(n)	(%)	95% CI*	(n)	(n)	(%)	95% CI	(n)	(n)	(%)	95% CI
2006	1	846	0.12	0.01 to 0.58	1	813	0.12	0.01 to 0.61	2	1659	0.12	0.02 to 0.40
2007	3	753	0.40	0.10 to 1.08	0	742	0.00	0.00 to 0.40	3	1495	0.20	0.05 to 0.55
2008	2	785	0.25	0.04 to 0.84	1	706	0.14	0.01 to 0.70	3	1491	0.20	0.05 to 0.55
Total	6	2384	0.25	0.10 to 0.52	2	2261	0.09	0.01 to 0.29	8	4645	0.17	0.08 to 0.33

* CI, confidence interval

Patients with positive results were treated with oral metronidazole in the first instance. The electronic notes of these 83 patients were then examined to determine those who had undergone a primary total hip or knee replacement. Eight patients were identified. A departmental database was used to create a control group of patients undergoing a primary hip or knee replacement, matched for surgeon, age to within three years, gender and month of operation. For each patient with CDAD three controls were selected. Where multiple possible controls existed, three were selected using a random number table. All patients had their prosthesis inserted by, or under the supervision of, a consultant orthopaedic surgeon. The hip replacement components in use during this period were the Exeter (Stryker, Newbury, United Kingdom), Corail (DePuy, Leeds, United Kingdom) or Olympia (Biomet UK, Bridgend, United Kingdom). The acetabular components were the Contemporary (Stryker) or Duraloc (DePuy). Cemented components were inserted using antibiotic-loaded polymethylmethacrylate bone cement (Palacos R&G Heraeus Medical, Wehrheim, Germany, or Simplex, Stryker). The total knee prostheses in use were the PFC Sigma (DePuy), Kinemax or Triathlon (Stryker). The same cements were used. Data regarding the total number of knee and hip replacements performed during the period in our institution were obtained from the mandatory coding dataset that was completed for all in-patient attendances. Case notes were obtained for all these patients and inspected to confirm the peri-operative antibiotic regimen and to determine comorbidity using the Charlson score;[14] pre- and post-operative prescription of gastroprotective agents; additional antibiotic prescription in the post-operative in-patient period; and the occurrence of surgical or medical complications (cardiovascular, respiratory, cerebrovascular, infectious, thromboembolic).

Statistical analysis. Data were analysed with SPSS version 13 (SPSS Inc., Chicago, Illinois). Incidences were calculated with 95% confidence intervals (CI). Fisher's exact chi-squared tests were used to examine the difference in proportions between the study group and the control group for the categorical variables of gastroprotective agent (H_2 antagonist or proton pump inhibitor) use, antibiotic use and complications. As Charlson scores were not normally distributed, a Mann-Whitney U test was performed to examine differences in comorbidity between groups. A p-value < 0.05 was considered statistically significant, and two-tailed tests were used throughout.

Results

Of the eight patients, six who underwent cemented total hip replacement (THR) and two who underwent cemented total knee replacement (TKR) had stool assays that were positive for *C. difficile* toxins A and B (Table I). Five of these patients were female. The overall incidence of CDAD was 0.17% (95% CI 0.08 to 0.33). The difference between the incidence of CDAD following THR and that following TKR was not statistically significant (Fisher's exact chi-squared, $p = 0.204$) (Table I). The median duration of hospital stay was longer (Mann-Whitney U test, $p < 0.001$) in those with CDAD (median = 10.5 days, interquartile range (IQR) 9 to 16) compared with those without (median = six days, IQR 5 to 6.75). The median time to onset of symptoms was six days (IQR 5 to 20).

There was no difference in comorbidity between those developing CDAD and the control group (Mann-Whitney, $p = 0.868$) (Table II). Four patients (50%) who developed CDAD had been prescribed a gastroprotective agent during their procedure, compared with ten (41.7%) in the control group (Mann-Whitney, $p = 0.703$). Four patients (50%) who developed CDAD had been prescribed additional antibiotics in the post-operative period, compared with three (12.5%) in the control group (Fisher's exact chi-squared, $p = 0.047$). Of these four patients, two had undergone TKR and two had undergone THR. In the group who developed CDAD, one received co-amoxiclav for a respiratory tract infection, one received trimethoprim for a urinary tract infection, one received vancomycin for an episode of methicillin-resistant *Staphylococcus aureus* (MRSA) septicaemia, and one was prescribed a single dose of gentamicin during the removal of an indwelling urinary catheter. In contrast, the three patients in the control group who received additional antibiotics all received gentamicin in connection with urinary catheter insertion/removal in accordance with local policy. There was no difference between groups in the prevalence of complications (Fisher's exact, $p = 0.085$).

A power calculation was performed on the basis of an underlying incidence of CDAD of 0.17% in the population. Assuming a desired rate of CDAD of 0.1% (absolute risk

Table II. Demographics, comorbidities, gastroprotective agent use and antibiotic use associated with the development of *C. difficile* associated disease (CDAD)

	Study group (n = 8)	Control group: no CDAD (n = 24)	p-value
Demographic characteristics			
Mean age in years (range)	75.8 (65 to 82)	75.5 (62 to 85)	0.897
Gender (male, % group)	3 (*37.5*)	11 (*45.3*)	1.00
Total hip replacement*	6	16	
Total knee replacement†	2	8	
Comorbidity: Charlson score (n)			
0	5	12	
1	0	7	
2	1	5	
3	1	0	
4	0	0	
5	0	0	
6	1	0	
Charlson (median, range)	0 (0 to 6)	0.5 (0 to 2)	0.868
Overall gastric protection use (%)	4 (*50*)	10 (*41.7*)	0.703
Pre-operative use (%)	1 (*12.5*)	3 (*12.5*)	1.000
Post-operative proton pump inhibitor (%)	2 (*25*)	5 (*20.8*)	1.000
Post-operative H_2 antagonist (%)	1 (*12.5*)	2 (*8.3*)	1.000
Overall additional antibiotic use	4 (*50*)	3 (*12.5*)	0.047
Co-amoxiclav	1	0	0.250
Trimethoprim	1	0	0.250
Vancomycin	1	0	0.250
Gentamicin	1	3	1.000
Complications	3 (*37.5*)	2 (*8.3*)	0.085

reduction = 0.07%), an α error = 0.05 and power 80% to detect a significant difference, 43 198 patients would be necessary in each arm. Furthermore, 1429 patients would need to be treated by this new regimen to prevent one case of CDAD.

Discussion

The primary aim of this study was to determine the incidence of CDAD following primary total joint replacement. There has been a paucity of data in the literature, and reports include outcomes from heterogenous populations of orthopaedic patients. Our overall incidence of CDAD of 0.17% was very similar to that (0.16%) reported in a recent series.[1]

Our local antimicrobial policy specified the use of cefuroxime, a second-generation cephalosporin, for 24 hours (three doses). Antibiotic prophylaxis is fundamental to the reduction of primary peri-prosthetic infection and has been shown by meta-analysis to reduce the relative risk of wound infection by 81%.[15] The evidence on which our policy is based is from the Norwegian Arthroplasty Registry[16] and the recent Scottish Intercollegiate Guideline Network guidelines[17] recommending multiple dosing over 24 hours.

Despite a multitude of studies, there is no clear evidence of the superiority of a multiple-dose regimen compared with a single-dose one, but patients having three or four peri-operative doses have the lowest risk for re-operation (for all reasons) at ten years.[16] There is no overwhelming evidence regarding the agent of choice. A systematic review examined single-dose *versus* extended-dose prophylaxis in preventing infection after internal fixation of fractures and showed no superiority of the extended regimen in preventing infection.[18] It did, however, estimate that a study would require 14 000 patients per treatment arm to be adequately powered to demonstrate a significant reduction in infection rates. A recent study[19] demonstrated that a change from three doses of cefuroxime to a single dose of cefuroxime and gentamicin at induction reduced the incidence of *C. difficile* in hip fracture patients. However, the study's design and the co-variables cast doubt over the validity of the conclusion. The study consisted of a retrospective review of infection rates before and after a change from multiple doses of cefuroxime to a single administration of gentamicin and cefuroxime. It could not be definitively shown that the reduction in *C. difficile* was due solely to the reduction to one dose of cefuroxime, and it may have been due to the addition of gentamicin, or to general changes in infection control measures. There is evidence to show that just one administration of a cephalosporin may cause colonisation and the detection of *C. difficile* toxin.[20,21] There is, however, evidence to show similar associations between CDAD and the administration of other agents from the β-lactam group,

and also from other groups such as the fluoroquinolones.[6,22]

Potential prophylactic regimens are considered by comparing their activity against organisms causing deep infection in patients with prosthetic joints (*Staph. aureus* and *S. epidermidis*) with their potential to cause adverse effects and colonisation with *C. difficile*. Ideally, agents are chosen that have a high efficacy against *C. difficile*, in order to prevent selection and resistance. Cephalosporins have a low prevalence of adverse reactions, with rashes occurring in up to 7% of those with penicillin hypersensitivity.[10] Rarer toxicities such as anaemia, skin reactions and hepatic dysfunction, are generally associated with longer term therapy.[10] Penicillins tend to have a higher rate of side effects, with anaphylactoid reactions occurring in 0.004% to 0.015% of patients.[10] Rashes can occur in up to 9% of patients.[10] The routine use of vancomycin for prophylaxis has been discouraged to prevent the selection of resistant strains of MRSA and *S. epidermidis*[1,10] and vancomycin-resistant enterococcus.

In this population, the administration of gastroprotective agents (proton pump inhibitors or H_2 receptor antagonists) was not associated with an increased risk of CDAD. In some populations[23,24] and in an experimental model[25] the administration of proton pump inhibitors has been shown to be an independent risk factor. The administration of antibiotics in addition to the prophylactic regimen was associated with an increased risk of CDAD, but no pattern of specific antimicrobial use could be identified. This was not associated with a difference in comorbidity as measured by the Charlson score,[14] or the incidence of complications.

This study was performed in a centre where a large number of primary arthroplasties are performed. A single antibiotic prophylaxis policy was used during the study period, and this allowed the elimination of variation of prophylaxis as a confounding factor. The disadvantages of this study were conferred by the low incidence of this condition in this group of patients, and the potential to make type II errors when comparing the effect of risk factors between groups. Furthermore, there may be a number of patients who develop symptoms of CDAD in the community after discharge in whom a formal diagnosis is not made. If symptoms are mild, stool samples may not be taken. This may become more significant in future as units aim to reduce the length of stay by early discharge programmes. Patients may also become colonised during their in-patient stay but remain asymptomatic. A later secondary insult, such as antibiotic prescription or illness, may lead to the development of CDAD. Future studies should assess gut flora colonisation with *C. difficile* following different antibiotic regimens. We were also unable to assess for environmental risk factors for *C. difficile*, such as the risk of direct transmission from one infected patient to another. It was not possible retrospectively to determine the particular bed-occupancy patterns of each patient and their respective controls.

This study confirmed the previously-reported very low incidence of CDAD in patients undergoing elective primary total joint replacement. We could not identify any association with comorbidity or the use of gastroprotective agents, but there was an association with the prescription of additional antimicrobial agents. Therefore, in primary joint arthroplasty decisions about the prevention of peri-prosthetic and surgical site infection with prophylactic antibiotics should be made primarily on the antibiotic susceptibility of organisms causing deep infections, the reduction of hypersensitivity reactions, and the lowest long-term rate of revision. Randomised controlled trials comparing the incidence of CDAD following competing prophylaxis regimens would be very costly and difficult to run, owing to the very large number of patients required. Cephalosporin agents have been used safely and should not be discarded without careful appraisal of these factors.

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