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Routine Use of Antibiotic Laden Bone Cement for Primary Total Knee Arthroplasty: Impact on Infecting Microbial Patterns and Resistance Profiles

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ABSTRACT

Antibiotic-laden bone cement (ALBC) is used in primary arthroplasties throughout Europe. In North America, ALBC is only FDA approved for revision arthroplasty after periprosthetic joint infection (PJI). No article has evaluated whether infecting microbial profile and resistance has changed with the introduction of ALBC. We hypothesized that prophylactic use of ALBC in primary total knee arthroplasty (TKA) has not had a significant impact on infecting pathogens, and antibiotic resistance profiles. A retrospective cohort analysis was conducted of all PJI patients undergoing primary TKA and total hip arthroplasty (THA) between January 2000 and January 2009. No significant change in the patterns of infecting PJI pathogens, and no notable increase in percentage resistance was found among organisms grown from patients with PJI that had received prophylactic antibiotic-loaded cement in their primary joint arthroplasty. Early findings suggest that routine prophylactic use of ALBC has not led to changes in infecting pathogen profile, nor has led to the emergence of antimicrobial resistance at our institution.

Antibiotic-laden bone cement (ALBC) prophylaxis has been used throughout Europe in both primary total knee arthroplasty (TKA) and primary total hip arthroplasty (THA) for decades. Based on 2007 figures, prophylactic ALBC has become the standard of care among European surgeons, particularly in Scandinavian countries [1]. This is due in large part to the Norwegian registry data on cemented total hip arthroplasty, which has demonstrated that the lowest rate of revision surgery, both for septic and aseptic failure, was found among patients receiving antibiotic containing cement plus systemic antibiotics [2].

In the United States, ALBC is not currently licensed for prophylactic use in primary joint replacement. At present, there are six different commercial preparations available, which are only licensed for use during the second stage of a two stage exchange arthroplasty [3]. Despite this, an increasing number of orthopedic surgeons in the United States have adopted the practice of routine addition of low dose antibiotic to cement for use in primary knee arthroplasty. In a 1995 survey, it was found that anywhere from 10–13% of US orthopaedic surgeons always use ALBC during their primary THA or TKA[4]. Presumably, this rise in use is due to the desire to prevent a periprosthetic infection[5,6],as well as avoid the resultant morbidity and costs associated from treating them[7].

The theoretical and documented benefits of prophylactic ALBC have to be weighed against the potential adverse effects of its use. Opponents of its use in the setting of primary total joint arthroplasty point to the following potential drawbacks: cost; effect on mechanical properties of cement; systemic toxicity; allergic reactions; and bacterial resistance [8–10]. While there is some *in vitro* data to suggest that prolonged exposure of organisms to sub-inhibitory levels of antibiotics encourages mutational adaptations that confer resistance [11,12], there remains little clinical evidence to support this theory.

The study aims to investigate whether the introduction of ALBC prophylaxis for primary total knee arthroplasty cases resulted in any significant changes in infecting microbial patterns and resistance profiles of organisms cultured in PJI cases at one North American institution. The hypothesis of this study is that the routine prophylactic use of antibiotic-laden cement in primary TKA has not had a significant impact on the resistance patterns of pathogens cultured from subsequent periprosthetic joint infections.

Materials and Methods

This retrospective cohort study was conducted upon receiving institutional review board (IRB) approval. All patients treated for a

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periprosthetic joint infection (PJI) of either knee or hip between January 1, 2000 and December 31, 2009 were identified through our institutional database by using appropriate billing codes for PJI. Of these cases, only patients that had a primary arthroplasty performed at this institution between the respective dates were included, in order to ensure that the nature of the cement (if any) used during the index arthroplasty would be known. This study centre has used Simplex P infused with 1.2 g Tobramycin (Stryker, Mahwah, NJ) in all total knee arthroplasty (TKA) procedures since mid 2003. Prior to this, cement which contained no antibiotic was used. All total hip arthroplasties performed at our centre between January 1, 2000 and December 31, 2009 were performed with cementless components. We feel that this group of total hip arthroplasty patients represents an appropriate internal control for our total knee arthroplasty cohort, since the surgeons and the perioperative patient care protocols were consistent across groups, and the only surgical factor that differed between the cohorts was the use of cement. Therefore, any potential variations in infecting pathogen profiles and antibiotic resistance in the community and institution over this same time period not due to the introduction of antibiotic laden bone cement would be reflected in the data on the total hip arthroplasty cohort.

Between January 1, 2000 and December 31, 2009 (excluding year 2003) a total of 11,469 primary total hip arthroplasties and a total of 11,494 primary total knee arthroplasties were performed. During the ten year time period of the study, there was an overall reduction in the rate of periprosthetic joint infection (PJI) at our institution. The rate of PJI in total hip arthroplasty (THA) patients decreased from 0.6% (21/3,352) before 2003 to 0.4% (33/8,117, $P = 0.16$) after 2003. Similarly, the rate of PJI in the total knee arthroplasty (TKA) cohort decreased from 2% (61/3,053) to 0.7% (59/8,441, $P = 0.0001$) over these same time periods.

Overall, data from 174 patients (86 male, 88 female, mean age 64 years old) who developed PJI after primary total joint arthroplasty were collected and analyzed. Of these, 120 were knees and 54 were hips. The infected patients were organized into four groups based on type and timing of surgery: Cohort 1- TKA performed prior to 2003 (without ALBC) (n = 61/3,053, 2%) Cohort 2- TKA performed after 2003 (with ALBC) (n = 59/8,441, 0.7%); Cohort 3 – THA performed prior to 2003 (control) (n = 21/3,352, 0.6%); and Cohort 4 – THA performed after 2003 (control) (n = 33/8,117, 0.4%). All patients that had surgery performed during 2003 were excluded, in order to allow for the delay in universal adoption of ALBC by the surgeons. All surgeries were performed by the same arthroplasty fellowship trained surgeons, and the clinical care pathways, including use of perioperative antibiotics, were standardized for the institution. The culture results from each case were collected and the level of susceptibility to each antibiotic tested was analyzed. A minimum of 24 months of clinical follow-up was required, and the mean duration of follow-up for each of the four groups was 53.7, 55.7, 54.2, 55.6 months respectively. The mean duration from primary arthroplasty to presentation with PJI was 19.0, 13.8, 18.6, 6.2 months respectively.

Each admission for PJI was considered as an individual case. Using the new definition for PJI established by the Musculoskeletal Infection Society, cases were included if they satisfied the following criteria: Either (1) a sinus tract communicating with the prosthesis (2) a pathogen isolated from two separate tissue or fluid cultures OR (3) four of the following six criteria: Elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP); elevated synovial leukocyte count, elevated synovial neutrophil percentage (PMN%), presence of intraarticular purulence, isolation of a microorganism in one culture of periprosthetic tissue or fluid, or greater than 5 neutrophils per high power field observed from histologic analysis of tissue (×400 magnification) [13]. Cases were excluded if there was an obvious clerical error, if the infected joint did not match the primary joint (i.e. an infection of the hip with only a primary knee performed during the specified time, or an infection in the joint on the contralateral limb), or if no procedure was performed as a result of the infection.

Inclusion based on date of index arthroplasty and date of infection was standardized to ensure that the follow up period for patients was similar for each of the four groups. Each group included only patients that had their primary joint performed during a consecutive 3 year period (2000–2002 for the pre 2003 groups and 2004–2006 for the post 2003 groups) and had presented with PJI during a consecutive 6 year period (2000–2005 for the pre 2003 groups and 2004–2009 for the post 2003 groups).

Differences were evaluated with a chi squared analysis and Fisher's exact test performed by SPSS 16.0, and statistical significance was set at $P < .05$ (SPSS Inc, Chicago, IL).

Results

In total, there were 174 cases of PJI at our institution from 2000–2009, of which 143 (82%) were culture positive. Some cases of culture positive PJI grew more than one organism resulting in a total of 174 unique positive cultures Approximately two thirds of the PJI cases were due to either *Staphylococcus aureus* or *coagulase-negative Staphylococcus* (116, or 67% of culture positive cases) (Table 1 Infecting Organism Data by Cohort). The other, non-staphylococcal, organisms included pathogens such as *Enterococcus*, *Pseudomonas*, etc. with the next most common infecting organisms being Group B strep (n = 9) and *Enterococcus faecalis* (n = 8).

Neither the number of PJI cases caused by *S. aureus*, coagulase negative staphylococcal species, or non-staphylococcal species changed significantly following the introduction of ALBC. Prior to 2003, *S. aureus* was the infecting organism in 35 cases (20 TKA, 15 THA; or 46% of 76 total cases), while after 2003, *S. aureus* was the infecting pathogen in 41 cases (19 TKA, 22 THA; or 42% of 98 total cases, p =0.17). Similarly, *S. epidermidis* was the infecting organism in 14 cases (10 TKA, 4 THA, or 18% of 76 total cases) prior to 2003, while after 2003, *S. epidermidis* caused PJI in 26 cases (19 TKA, 7 THA or 27% of 98 total cases, p = 0.38) (Table 1 Infecting Organism Data by Cohort). The most common non staphylococcal species causing PJI prior to 2003 were Group B *Streptococcus* (n = 5 cases), and *Pseudomonas* (n = 5 cases). The GBS cohort had multiple resistance patterns, while all of the *Pseudomonas* strains were pan-sensitive to antibiotics. Following the introduction of ALBC in 2003, the most common non-*staphylococcal* species causing PJI were *E. faecalis* (n = 6 cases), Proteus (n = 4), and *Streptococcus pneumoniae* (n = 4). Of the PJI cases caused by *E. faecalis*, 4 were vancomycin sensitive and 2 were vancomycin resistant. All of the *S. pneumoniae* cases were pan-sensitive species, while all of the *Proteus* infections were resistant to tetracycline but sensitive to all other antibiotics (data not shown).

We focused our statistical analysis on the antibiotic resistance patterns among *S. aureus* and coagulase-negative *Staphylococcus*, since they represented the majority of the infecting pathogens. The percentage resistances to methicillin, erythromycin and tetracycline in the staphylococcal species are outlined in the following table. (Table 2 Resistance Profiles of Staph Species by Cohort). In the control cohort of cementless THA patients, there was a non-significant increase in methicillin resistance after 2003 (53–55%, p = 0.86), representing the change in the baseline community and institutional microbial resistance patterns. In the TKA cohort, following the introduction of ALBC, the overall percentage of methicillin resistant cases decreased from 63% to 47% (p = 0.19). Notably, there was a statistically significant decrease in methicillin resistant *S. aureus* from 40% to 18% ($P = 0.048$), while there was a nonsignificant increase in methicillin resistant *S. epidermidis* infections from 23% to 29% (p =0.6). Represented a different way, the risk of developing MRSA infection following