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ORIGINAL ARTICLE

Does antibiotic bone cement reduce infection rates in primary total knee arthroplasty?

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Abstract

Introduction Infection after total knee arthroplasty (TKA) impacts the patient, surgeon, and healthcare system significantly. Surgeons routinely use antibiotic-loaded bone cement (ALBC) in attempts to mitigate infection; however, little evidence supports the efficacy of ALBC in reducing infection rates compared to non-antibiotic-loaded bone cement (non-ALBC) in primary TKA. Our study compares infection rates of patients undergoing TKA with ALBC to those with non-ALBC to assess its efficacy in primary TKA.

Methods A retrospective review of all primary, elective, cemented TKA patients over the age of 18 between 2011 and 2020 was conducted at an orthopedic specialty hospital. Patients were stratified into two cohorts based on cement type: ALBC (loaded with gentamicin or tobramycin) or non-ALBC. Baseline characteristics and infection rates determined by MSIS criteria were collected. Multilinear and multivariate logistic regressions were performed to limit significant differences in demographics. Independent samples *t* test and chi-squared test were used to compare means and proportions, respectively, between the two cohorts.

Results In total, 9366 patients were included in this study, 7980 (85.2%) of whom received non-ALBC and 1386 (14.8%) of whom received ALBC. There were significant differences in five of the six demographic variables analyzed; patients with higher Body Mass Index (33.40 ± 6.27 vs. 32.09 ± 6.21; kg/m^2) and Charlson Comorbidity Index values (4.51 ± 2.15 vs. 4.04 ± 1.92) were more likely to receive ALBC. The infection rate in the non-ALBC was 0.8% (63/7,980), while the rate in the ALBC was 0.5% (7/1,386). After adjusting for confounders, the difference in rates was not significant between the two groups (OR [95% CI]: 1.53 [0.69–3.38], $p = 0.298$). Furthermore, a sub-analysis comparing the infection rates within various demographic categories also showed no significant differences between the two groups.

Conclusion Compared to non-ALBC, the overall infection rate in primary TKA was slightly lower when using ALBC; however, the difference was not statistically significant. When stratifying by comorbidity, use of ALBC still showed no statistical significance in reducing the risk of periprosthetic joint infection. Therefore, the advantage of antibiotics in bone cement to prevent infection in primary TKA is not yet elucidated. Further prospective, multicenter studies regarding the clinical benefits of antibiotic use in bone cement for primary TKA are warranted.

Keywords Primary total knee arthroplasty · Antibiotic-loaded bone cement · Periprosthetic joint infection

Introduction

Periprosthetic joint infection (PJI) is one of the most severe and devastating complications following total joint arthroplasty (TJA) [1]. Despite an overall incidence of 2.0–2.4% in total hip arthroplasty (THA) and total knee arthroplasty (TKA), the cost of treating PJI was $566 million in 2009 and is projected to be $1.85 billion by 2030 ($753.4 million for THA and $1.1 billion for TKA) [1, 2]. As a preventive measure, common antibiotics used in bone cement during primary TKA include gentamicin and tobramycin, two broad

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spectrum aminoglycosides effective against both gram-negative and some gram-positive bacteria, and vancomycin, a glycopeptide effective against gram-positive bacteria [3].

Antibiotic-loaded bone cement (ALBC) is comprised of polymethylmethacrylate (PMMA), a synthetic resin, impregnated with antibiotic for elution into surrounding tissue to help prevent infection [3]. Prophylactic use of ALBC in primary TJA may mitigate risk of postoperative infection; however, its efficacy remains unclear and controversial. Antibiotic resistance after prolonged exposure, cost, toxicity, release kinetics, and implant loosening must be considered as potential issues when using ALBC [4]. Prophylactic ALBC is commonly used in Europe but not in the United States. The Food and Drug Administration has approved the use of ALBC in patients receiving revision TJA but not in primary TJA which has led to off-label usage of the product [5].

A study conducted by Espehaug et al. initially suggested that systemic prophylactic antibiotics combined with ALBC for prosthetic fixation reduced risk of revision when compared to systemic antibiotics or ALBC alone following THA [6]. A subsequent meta-analysis of primary TKA performed by the same group suggests that ALBC use may be associated with increased PJI risk in the early postoperative period when compared with non-ALBC cement; however, this finding may reflect selection of higher-risk patients for ALBC [7].

To our knowledge, data on this topic is limited and only two randomized controlled trials (RCT) have investigated the efficacy of ALBC in reducing PJI risk following primary TKA [8, 9]. Leta et al. have published a protocol proposal for a large RCT (the ALBA study) in which a minimum of 9172 patients undergoing full-cemented primary TKA at Norwegian hospitals will be randomized into ALBC and non-ALBC cohorts to investigate risk of revision surgery due to PJI at 1 year follow up [10]; however, this study has not begun. The purpose of our study was to determine whether primary TKAs using ALBC had a lower incidence of PJI compared to TKAs using non-ALBC.

Methods

A retrospective review of all primary, elective, cemented TKA patients over the age of 18 between 2011 and 2020 was conducted at an urban, orthopedic specialty hospital. Patients were stratified into two cohorts based on cement type: ALBC (loaded with gentamicin or tobramycin) or non-ALBC (bone cement without antibiotics). For ALBC with gentamicin, our institution used either Simplex HV with gentamicin (Stryker, Mahwah, NJ) or Refobacin Bone Cement R (Zimmer Biomet, Warsaw, IN); for ALBC with tobramycin, we used Simplex P with tobramycin (Stryker, Mahwah, NJ). Cement containing antibiotics were pre-mixed and pre-packaged by the manufacturer; additional antibiotic powder was not added in the OR. The Simplex HV kit with gentamicin and tobramycin is on average 52% less expensive than the Refobacin Bone Cement R kit.

Infection rates were initially screened and identified using International Classification of Disease, Ninth (ICD-9) and Tenth Revision (ICD-10) diagnosis codes 996.69 and T84.5. Suspected PJIs were then further verified using the Musculoskeletal Infection Society (MSIS) criteria [11]. The primary outcome was a comparison of infection rates between primary TKA patients who received implants with ALBC and those with non-ALBC. The secondary outcome was a comparison of infection rates between the two cohorts within various demographic sub-divisions.

All primary TKAs were performed in standard operating rooms and similar staffing were present during all cases. All scrubbed personnel were required to wear a surgical helmet and hood. Patients also underwent nasal MRSA colonization screening. If positive, either topical chlorhexidine or mupirocin was applied intranasally for 5 days or povidone iodine was applied intranasally one time prior to surgery. All patients were instructed to use 2% chlorhexidine gluconate wipes the night before surgery and morning of surgery to decolonize the skin. During surgery, skin prep was performed with 2% chlorhexidine gluconate in 70% isopropyl alcohol solution (ChloraPrep; Carefusion, USA). Hair was also removed from the incision site in the preoperative holding area to maximize sterility and mitigate infection risk.

All patients received weight-based cefazolin every 8 h for 24 h with the first dose within 60 min of skin incision. Patients with a confirmed severe penicillin or cephalosporin allergy received one preoperative dose of clindamycin with vancomycin perioperatively. If methicillin-resistant *Staphylococcus aureus* (MRSA) was positive on nasal culture prior to surgery, a weight-based dosing regimen (15–20 mg/kg) of vancomycin with a gram-negative agent (one dose of 2 g of aztreonam if aged 75 years and older; $\geq$ 120 kg, or creatinine clearance $<$ 20 ml/min, or 3 to 5 mg/kg of gentamicin) was administered prior to incision. Cefazolin or vancomycin was given for 24 h postoperatively; for patients who received clindamycin, additional dosages of clindamycin were given.

In January 2014, our institution implemented an infection prophylaxis protocol for high-risk TKA patients, known as the Vancomycin-Povidone Iodine Protocol (VIP), [12] defined by Iorio et al. The protocol consists of a 0.35% povidone-iodine (17.5 mL in 500 mL saline) lavage which poured into the deep wound and left for 3 min after the final implants are placed [13]. After lavage, 1 L of sterile saline is introduced via pulsed irrigation. One gram of vancomycin powder is then placed deep to the fascia and 1 g is placed superficial to the fascia. It was not recorded whether antibiotic was rubbed into the muscle, fascia, and subcutaneous

tissue due to variability among surgeons. Wound closure and dressing types were left to surgeon discretion. In January 2016, all TKA patients began receiving VIP irrespective of risk.

Baseline demographic information such as age, sex, BMI, American Society of Anesthesiologists (ASA) class, Charlson Comorbidity Index (CCI), smoking status, and diabetes status were collected via manual chart review and compared between the two groups (Table 1). These measurements were selected to comprehensively evaluate preoperative demographic differences between the ALBC and non-ALBC cohorts.

Statistical analysis

All data were extracted from our institution's large electronic database (Epic Caboodle. version 15; Verona, WI) and were de-identified on encrypted Microsoft Excel software. Multilinear and logistic regressions were performed to limit significant differences in demographics. Independent samples *t* tests and chi-squared tests were used to compare means and proportions, respectively, between the two cohorts. All statistical analyses were performed using SPSS v25 (IBM Corporation, Armonk, NY). Results were considered statistically significant if $P < 0.05$. The present study was exempt from human subjects review by our institutional review board as part of our institutional quality improvement program. No external funding was received for any aspect of this work.

Table 1 Demographic comparison

	Non-ALBC	ALBC	*P* value
Age (years)	65.88 ± 9.78	65.81 ± 10.17	0.815
Gender			0.003
Female	5339 (66.9%)	983 (70.9%)	
Male	2641 (33.1%)	403 (29.1%)	
BMI (kg/m^2)	32.09 ± 6.21	33.40 ± 6.27	< 0.001
ASA Score			< 0.001
1	184 (2.3°%)	15 (1.1%)	
2	4528 (56.8%)	586 (42.3%)	
3	3126 (39.2°%)	747 (53.9%)	
4	135 (1.7%)	38 (2.7%)	
Smoking status			0.028
Never smoker	4668 (58.5%)	858 (61.9%)	
Former smoker	2734 (34.3%)	418 (30.2%)	
Current smoker	520 (6.5%)	100 (7.2%)	
Unknown	58 (0.7%)	10 (0.7%)	
CCI	4.04 ± 1.92	4.51 ± 2.15	< 0.001
Diabetes			< 0.001
Diabetic	1457 (18.3%)	516 (37.2%)	
Non-Diabetic	6523 (81.7%)	870 (62.8%)	

Results

In total, 9366 patients were included in this study, 7980 (85.2%) of whom received non-ALBC and 1386 (14.8%) of whom received ALBC. Non-ALBC patients were on average 65.88 ± 9.78 years of age, with a mean BMI of 32.09 ± 6.21 kg/m^2 and average CCI scores of 4.04 ± 1.92. They were also mostly female (66.9%), non-diabetic (81.7%), and non-smokers (56.8%), with majority having had a preoperative ASA score of 2 (56.8%) (Table 1). While ALBC patients were similar in age (65.81 ± 10.17 years; $p = 0.815$), they were significantly different in all the other demographic characteristics ($p < 0.05$) (Table 1). ALBC patients were slightly more obese with a BMI of 33.40 ± 6.27 kg/m^2 and had higher average CCI scores of 4.51 ± 2.15. They were mostly female (70.9%), non-diabetic (62.8%), and non-smokers (61.9%), with majority having had a preoperative ASA score of 3 (53.9%) (Table 1). The demographic differences noted here, while statistically significant, may also be clinically relevant as certain comorbidities such as obesity and diabetes are known to impact outcomes in primary TKA.

Of the 7980 patients who received non-ALBC, 63 (0.8%) developed an infection (Table 2). Of the 1386 patients who received ALBC, 1379 (99.5%) did not develop an infection while 7 (0.5%) developed an infection (Table 2). A multivariate logistic regression controlling for confounders revealed that the difference in infection rates was not significant even though there was an increased odds ratio of developing an infection in the non-ALBC cohort compared to the ALBC cohort (OR [95% CI]: 1.53 [0.69–3.38], $p = 0.298$) (Table 2).

Secondarily, we conducted a sub-analysis comparing the infection rates within various demographic categories (Table 3). Multivariate logistic regressions were performed to control for demographic confounders and no significant

Table 2 Infection Rates between Cement w/ and w/o Abx

	Non-ALBC	ALBC	Total	Odds ratio (95% CI)	*P* value
Infection				1.53 (0.69–3.38)	0.298
No	7917 (99.2%)	1379 (99.5%)	9296 (99.3%)		
Yes	63 (0.8%)	7 (0.5%)	70 (0.7%)		
Total	7980	1386	9366		

Table 3 Comparison of infection rates within various demographic sub-divisions

Demographics	Non-ALBC		ALBC		Odds ratio (95% CI)	*P* value
	# of patients infected (%)	Total no. of patients	# of patients infected (%)	Total no. of patients		
Gender						
Female	33 (**0.6**)	5339	3 (**0.3**)	983	2.00 (0.60–6.63)	0.257
Male	30 (**1.1**)	2641	4 (**1.0**)	403	1.16 (0.40–3.39)	0.781
BMI						
BMI < 30	21 (**0.7**)	3128	5 (**1.2**)	424	0.61 (0.22–1.66)	0.33
BMI > 30	41 (**0.9**)	4627	2 (**0.2**)	921	3.84 (0.92–16.08)	0.065
BMI: 30 to 34.9	25 (**1.1**)	2362	0 (**0.0**)	411	N/A	N/A
BMI: 35 to 39.9	6 (**0.4**)	1421	2 (**0.6**)	315	0.59 (0.11–3.07)	0.531
BMI > 40	10 (**1.2**)	844	0 (**0.0**)	195	N/A	N/A
ASA						
1	2 (**1.1**)	184	1 (**6.7**)	15	0.28 (0.003–22.57)	0.57
2	29 (**0.6**)	4528	2 (**0.3**)	586	1.83 (0.43–7.79)	0.411
3	30 (**1.0**)	3126	2 (**0.3**)	747	3.16 (0.75–13.37)	0.118
4	2 (**1.5**)	135	2 (**5.3**)	38	0.372 (0.02–9.13)	0.545
Smoking status						
Never smoker	26 (**0.6**)	4668	3 (**0.3**)	858	1.69 (0.50–5.76)	0.4
Former smoker	30 (**1.1**)	2734	2 (**0.5**)	418	2.13 (0.50–9.10)	0.306
Current smoker	7 (**1.3**)	520	2 (**2.0**)	100	0.84 (0.16–4.38)	0.836
CCI						
0	0 (**0**)	26	0 (0)	3	N/A	N/A
1 or 2	10 (**0.7**)	1337	1 (**0.7**)	150	1.22 (0.15–9.85)	0.852
3 or 4	32 (**0.8**)	4261	4 (**0.6**)	679	1.29 (0.45–3.74)	0.636
> 5	21 (**0.9**)	2356	2 (**0.4**)	554	2.17 (0.50–9.42)	0.301
Diabetes	8 (**0.5**)	1457	2 (**0.4**)	516	1.45 (0.30–6.95)	0.641

differences in infection rates were found between the two groups in any of the demographic sub-categories ($p > 0.05$). Additional details regarding the full results of the sub-analysis, including the odds ratios and *p* values for each comparison, can be found in Table 3.

Discussion

Although the efficacy of high dose ALBC has been thoroughly investigated in the treatment of PJI, low dose use for primary TKA PJI prophylaxis is still debated. As of 2016, more than 90% of surgeons routinely use ALBC for prophylaxis in primary TKA in the United Kingdom, Norway, and Sweden whereas only 10% do in the United States [14]. Clinical studies present conflicting data, and to our knowledge, only two randomized controlled trials have assessed its value in TKA [8, 9]. According to a meta-analysis conducted by Zhang et al. in 2019, many suggest that ALBC acts primarily to reduce deep surgical-site infection rates, as systemic antibiotics have less tissue penetration; however, ALBC is not as effective in reducing superficial infection rates [15]. Data from the Norwegian national register indicates that ALBC confers a protective effect against infection in THA, but the effect in TKA remains controversial [6]. Sultan et al. propose that ALBC use is more applicable in TKA due to the higher percentage of cemented prostheses compared to THA [16]. As a result, the use of ALBC in primary TKA may have more significant implications. Therefore, the goal of this study was to determine the value and utility of ALBC in primary TKA. Our findings showed no statistically significant difference in infection rates between the ALBC and non-ALBC groups, even when controlling for demographic variables.

Multiple studies have supported the value of using prophylactic ALBC in primary TKA. After controlling for baseline demographic factors, we found no difference in infection rates between the two groups. A retrospective study conducted by Bendich et al. investigated outcomes of 15,972 veterans who had primary TKA with either ALBC or non-ALBC [17]. At 5 year follow up, TKAs with ALBC had lower all-cause revision rate compared to those with non-ALBC (5.3% vs. 6.7%, $p = 0.0009$) and a lower rate of revision for PJI (1.9% vs. 2.6%, $p = 0.005$). Similarly, Eveillard et. al determined in a prospective study that gentamicin-impregnated bone cement may be effective in preventing

deep wound infection after TKA, although it did not reach statistical significance (9.51% non-ALBC vs. 1.21% ALBC, $p=0.07$) [18].

Other studies recommend against routine use of ALBC [9, 19–21]. An RCT conducted by Hinarejos et al. reported that erythromycin and colistin-loaded bone cement in primary TKA did not lead to a decrease in the rate of infection compared to systemic prophylactic antibiotic administration (1.37% vs. 1.35%, $p=0.96$) [9]. Anis et al. performed a retrospective review of primary TKAs between 2014 and 2017 and found that PJI rates were higher in the ALBC cohort compared to the non-ALBC cohort (1.0% vs. 0.5%, $p<0.001$) [19]. Similarly, Wang et al. performed a retrospective review that compared the rates of deep infection in gentamycin-impregnated bone cement versus non-ALBC and found that ALBC did not predict lower infection rate at 1 year ($p=0.865$) [20]. In a large retrospective community knee registry study, Namba et al. found a higher rate of deep infection following primary TKA in patients who received ALBC compared to those who received non-ALBC (1.4% (28/2030) vs. 0.7% (9,154/20,869), $p=0.002$); however, the study did not indicate type of ALBC, use of ultraclean air, concomitant systemic antibiotic usage [21]. Additionally, the ALBC group had a significantly higher number of diabetics, patients with an ASA class greater than three, and no-osteoarthritis diagnoses. We report similar findings to these studies and did not find statistical significance in outcomes between the two cohorts at our institution.

Comparison of all baseline demographic information yielded statistical significance between the two cohorts aside from age. Therefore, patients in our study who received ALBC were higher risk based on comorbidities. Preoperative risk can be assessed using different variables and scores, including ASA class, CCI, diabetes status, and smoking status. The ASA class and CCI are used to quantify a patient's overall health status. An ASA class greater than 2 or 3 is associated with a significantly higher risk for developing infection after TJA [22]. A CCI score greater than 4 is associated with 117% increased risk of developing infection after TKA compared to a score of 0 [23–25]. Kienzle et al. reviewed 100 patients who underwent total knee replacement revision due to PJI and demonstrated that risk of aseptic loosening and recurrent PJI was significantly increased in patients with higher preoperative ASA scores ($p=0.020$); however, CCI was moderately correlated with the prevalence of aseptic loosening ($r=0.40$) and recurrent PJI ($r=0.44$) [26]. Weaver et al. confirmed that discrepancies exist between ASA class and CCI but concluded that preoperative comorbid conditions are associated with poorer outcomes after TJA [27]. Additionally, they found that PJI occurred in 2.19% of patients with diabetes compared to 0.48% in non-diabetic patients after TKA. Lastly, tobacco is known to interfere with wound healing by reducing nutritional blood flow to the skin [28]. Bedard et al. performed a systematic review of 14 studies to assess the relationship between tobacco use and wound complications or PJI after TJA; they concluded that current tobacco users had a significantly higher risk of PJI (OR, 2.16 [1.57–2.97] compared to non-tobacco users and former tobacco users (OR, 1.52 [1.07–2.14]) [29]. As a result, careful attention must be paid to demographic information as it may impact outcomes in patients who receive ALBC in primary TKA.

Although patients are more likely to receive ALBC based on higher preoperative risk assessment in our study, we wanted to investigate whether ALBC use affected PJI risk in patients with the same comorbidity burden. In a demographic sub-analysis, we compared infection rates between ALBC and non-ALBC groups using stratified comorbidity data. ALBC did not mitigate infection rates following primary TKA in patients of the same ASA class, CCI, smoking status, BMI ranges, or diabetes status. However, studies show that a BMI > 40 kg/m^2 increases the risk of infection by 3.3 times and a BMI > 50 kg/m^2 increases the risk of infection by 21 times following primary TJA [30, 31]. In a single-center review of 7181 TJAs, Jämsen et al. found that infection rate increased from 0.37% in patients with normal BMI to 4.66% in patients with morbid obesity [32]. They also found that diabetes doubled PJI risk independent of obesity and that morbidly obese patients with diabetes had the highest risk (9.8%); however, the study combined THA and TKA in the analysis. We did not find a significant association between ALBC use in diabetic patients or various BMI levels and PJI risk. Nevertheless, as BMI has a strong correlation to diabetes, surgeons should consider the potential benefit of ALBC in this patient population as well [33, 34]. Based on the literature reviewed for this study, current evidence to support ALBC use among other comorbidities is equivocal.

This study had several limitations. First, the groups were unbalanced which decreases the power of the *t* tests performed and limits statistical significance. Second, use of prophylactic vancomycin powder became standard of care at our institution during the study period which could impact risk for potential infection in both ALBAC and non-ALBC patients. Lastly, although we included a large sample size, our study design may not be sufficiently powered. Nevertheless, our analysis suggests that prophylactic use of ALBC may not confer an added benefit for all comorbidities in primary TKA but further analyses must be conducted to investigate its utility and the value of demographic information in mitigating PJI risk.

Conclusion

The effectiveness of ALBC in primary TKA remains controversial. Compared to the non-ALBC cohort, the infection rate in primary TKA was slightly lower when using ALBC;

however, the difference was not statistically significant. Demographic information between the two cohorts was significantly different in all categories except age. After stratifying patients by comorbidity, there was still no significant difference in the use of ALBC to reduce PJI risk. ALBC may not be indicated for all patients; however, the benefits of its use in various patient demographic groups needs to be evaluated. Future multicenter studies are warranted to evaluate the clinical benefits of routine antibiotic use in bone cement for different patient populations.

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Declarations

Conflict of interest Mr. Cieremans declares that he has no conflict of interest. Mr. Muthusamy declares that he has no conflict of interest. Dr. Singh declares that he has no conflict of interest. Dr. Rozell is on the editorial board for the Bulletin of the Hospital for Joint Diseases and a district 1 delegate of the New York State Society of Orthopaedic Surgeons. Dr. Aggarwal has received consulting fees from Zimmer Biomet and research support from Zimmer Biomet. Dr. Schwarzkopf has received research grants from Smith&Nephew and Intelijoint, royalties from Smith&Nephew, consulting fees from Smith&Nephew and Intelijoint, and stock in Intelijoint, Gauss Surgical, and PSI. He is a board member of AAOS and AAHKS and on the editorial board of JOA and Arthroplasty Today. None of these COI are relevant to this work.

Ethics approval An approval by an ethics committee and informed consent were not applicable for this study. The present study was exempt from human subjects review by our institutional review board as part of our institutional quality improvement program.

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