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Efficacy of Adjunctive Antibiotic-Loaded Acrylic Bone Cement for Deep Surgical Site Infection Prophylaxis after Primary Cemented Hip and Knee Arthroplasties

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Abstract

Purpose: The efficacy of antibiotic-loaded acrylic bone cements (ALBC) for prophylaxis of deep surgical site infections (deep SSIs) after primary cemented joint replacement surgery remains controversial. Therefore, the purpose of this study was to examine the issue, with respect to three types of arthroplasty, namely, total knee arthroplasty (TKA), total hip arthroplasty (THA), and bipolar hip arthroplasty (BHA).

Methods: The records of 1,138 patients who received primary cemented TKAs, THAs, and BHAs between January 2006 and May 2013 were retrospectively reviewed. ALBC was used in 558 cases (ALBC group), and non-antibiotic-loaded acrylic bone cement was used in 580 cases (non-ALBC group). A logistic regression analysis was performed to determine the influence of ALBC on the incidence of SSI and to determine the risk factors associated with SSI.

Results: The overall rate of deep SSI was 0.97% (1.4% in the ALBC group and 0.5% in the non-ALBC group), with the difference not being significant. Results of multivariate logistic regression analysis with the stepwise selection method showed that diabetes mellitus was one of the risk factors associated with the incidence of deep SSI after surgery.

Conclusions: In the study population, ALBC did not prevent deep SSIs in primary cemented joint replacement, regardless of the type of joint replacement and whether or not the patient was diabetic.

Keywords

Antibiotic-loaded acrylic bone cement, Primary arthroplasty, Infection, Prophylaxis, THA, TKA

Abbreviations

ALBC: Antibiotic-loaded acrylic bone cement; SSI: Surgical site infections; TKA: Total knee arthroplasty; THA: Total hip arthroplasty; BHA: Bipolar hip arthroplasty; CDC: Centers for disease control and prevention; BMI: Body mass index; DM: Diabetes mellitus; RA: Rheumatoid arthritis; CRF: Chronic renal failure; MRCNS: Methicillin-resistant coagulase negative *Staphylococcus*; MRSA: Methicillin-resistant *Staphylococcus aureus*; RCT: Randomized controlled trial

Introduction

Deep surgical site infection (SSI) following arthroplasty is a devastating complication and often requires revision surgery with high cost, increased complexity, and prolonged hospitalization [1]. In most cases, removal of the prosthesis is needed. Systemic antibiotics to prevent deep SSIs are recommended by the Centers for Disease Control and Prevention (CDC) guidelines [2]. However, because of impaired blood circulation, the administered antibiotics may not reach an effective concentration at the site of the implant to eradicate deep SSIs [3].

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Antibiotic-loaded acrylic bone cement (ALBC) was first introduced to the field of arthroplasty by Buchholz and Engelbrecht in 1970 [4]. Recently, ALBC has been recognized as one of the most practical local drug delivery methods in cemented total joint arthroplasty [5]. Prophylactic administration of ALBC in cemented primary arthroplastiesis a common adjunctive practice in many countries, such as the United Kingdom [6], Norway [7,8], and Sweden [9]. Using Norwegian Arthroplasty Registry data, Espehaug, et al. [7] and Engesaeter, et al. [8] showed that systemic antibiotics combined with ALBC led to fewer revisions than other methods, such as systemic only or ALBC only. Meta-analyses by Parvizi, et al. [10] and by Wang, et al. [5] demonstrated the effectiveness of ALBC with a large number of THA and TKA cases, respectively.

However, several studies showed different results. McQueen, et al. [11] found no significant difference in the incidence of early superficial or deep infections, whether or not the cement contained antibiotics. Hinarejos, et al. [12] conducted a randomized controlled trial (RCT) with 2948 cemented TKAs and concluded that the use of ALBC did not lead to a decrease in the rate of infection. Other related reports documented that addition of antibiotics may reduce the shear strength of the cement [13] and induce drug-resistance [14,15].

While there are arguments for and against ALBC, Jiranek, et al. [16] and Parvizi, et al. [17] admit the effectiveness of ALBC, but recommended that use of ALBC in primary arthroplasty be limited to patients at high risk of deep SSIs, such as those with DM or immunosuppressed conditions. In support of this recommendation, Chiu, et al. [18] reported a significant decrease in the infection rate in DM patients when ALBC was used in an RCT.

Therefore, more research and clinical data are needed to address the efficacy of ALBC in preventing deep SSI after primary cemented arthroplasty. The purpose of the current study was to provide clinical data on this issue, with respect to three types of cemented arthroplasties.

Patients and Methods

Study groups

The records of 1,138 consecutive patients who underwent primary cemented total knee arthroplasty (TKA), total hip arthroplasty (THA), and bipolar hip arthroplasty (BHA) between January 2006 and May 2013 were retrospectively reviewed. The patients were divided into two groups: those who had undergone surgery between January 2006 and June 2009 and received ALBC (100 mg of amikacin sulfate per 40 g of bone cement) (ALBC group; 558 patients) and those who had undergone surgery without ALBC between July 2009 and May 2013 (non-ALBC group; 580 patients). Demographic characteristics of the patients are listed in Table 1. Except for the local antibiotic delivery, the same protocol for systemic antimicrobial prophylaxis was used in both groups, that is, preoperative intravenous prophylactic antibiotics were administered with 1 g of cefazolin with induction of anesthesia, followed by 1 g of cefazolin every six hours for the first twenty-four hours after surgery. Based on CDC guidelines [2], deep SSIs that had been identified within one postoperative year were included in the study but superficial SSIs were excluded.

The rate of deep SSI was compared between the two groups. Demographic data, including age, sex, body mass index (BMI), and the prevalence of co-morbidities (diabetes mellitus (DM), rheumatoid arthritis (RA), and chronic renal failure (CRF)) were also recorded to study the risk factors associated with deep SSI. The Committee for the Ethics of Human Research of Hakodate Central General Hospital approved the study protocol, and informed consent was obtained from each of the patients whose records were included in the study.

Statistical analysis

Sample size was calculated thus. Accepting an alpha risk of 0.05 and a beta risk of 0.20 in a two-sided test for two independent proportions, it was calculated that

Table 1: Demographic characteristics of the two groups by use of ALAC.

Variable	ALBC group	Non-ALBC group	p value
Number of patients	558	580	
TKA	300 (53.8%)	270 (46.6%)	
THA	151 (27.1%)	174 (30.0%)	
BHA	107 (19.2%)	136 (23.4%)	
Age [years]	72.3 (71.5-73.1)	73.5 (72.7-74.3)	0.04
Sex (M/F) [%]	14.5/85.5	15.9/84.1	0.56
BMI	25.3 (24.9-25.7)	25.0 (24.6-25.3)	0.23
Comorbidities [number of patients]			
Diabetes mellitus	110 (19.7%)	149 (25.7%)	0.02
Rheumatoid arthritis	37 (6.6%)	30 (5.2%)	0.32
Chronic renal failure	28 (5.0%)	23 (4.0%)	0.47

Continuous values (age and BMI) are expressed as means (95% confidence intervals).

Table 2: Details of all cases with infections.

No.	Age (y)	Sex	BMI (kg/m²)	DM	RA	CRF	Operation	ALBC	Days from operation	Infecting organisms
1	66	F	21.5	-	-	-	BHA	-	7	MRCNS
2	78	F	17.3	-	-	-	BHA	+	8	MRSA
3	49	F	26	-	-	-	THA	+	13	Negative culture
4	76	F	22.7	+	-	-	BHA	-	16	Negative culture
5	58	F	31.2	+	-	+	TKA	+	18	MRCNS
6	82	F	21.1	+	-	-	BHA	+	35	MRSA
7	82	F	25.1	+	-	-	TKA	+	42	MRSA
8	83	F	25.4	+	-	-	TKA	-	44	MRSA
9	76	F	32	+	-	-	TKA	+	64	MRCNS
10	77	F	25.9	-	-	-	THA	+	79	MRCNS
11	56	M	19.6	-	-	-	THA	+	86	MRSA

M: Male; F: Female; DM: Diabetes mellitus; RA: Rheumatoid arthritis; CRF: Chronic renal failure; MRCNS: Methicillin-resistant coagulase negative *Staphylococcus*; MRSA: Methicillin-resistant *Staphylococcus aureus*.

Table 3: Numbers and rates of infection.

Type of operation	ALBC group	Non-ALBC group	p value
TKA	300	270	
Infection	3 (1.0%)	1 (0.4%)	0.35
THA	151	174	
Infection	3 (2.0%)	0 (0%)	0.1
BHA	107	136	
Infection	2 (1.9%)	2 (1.5%)	0.59
Total	558	580	
Infection	8 (1.4%)	3 (0.5%)	0.1

Table 4: Multivariate model of risk factors for infection.

Variable	Odds ratio	p value
Antibiotic-loaded cement (+)	3.22	0.07
Age	0.97	0.36
Sex (F)	2.15	0.43
BMI	0.94	0.34
DM (+)	5.14	0.01
RA (+)	< 0.001 (unstable)	0.19
CRF (+)	1.27	0.83

p value for whole model: 0.10.

Table 5: Numbers and rates of infection in the two groups with and without diabetes mellitus.

Variable	Odds ratio	p value
Antibiotic-loaded bone cement (+)	3.17	0.07
DM (+)	4.57	0.02

p value for whole model: 0.01.

Table 6: Number and rates of infection with DM (+) and (-) groups.

DM	ALBC group	Non-ALBC group	p value
DM (+)	110	149	
Infection	4 (3.64%)	2 (1.34%)	0.23
DM (-)	448	431	
Infection	4 (0.89%)	1 (0.23%)	0.2

a minimum of 2,227 patients were needed in each of the two study groups in order to detect a decrease in the deep SSI incidence ratio from 2.3% in the ALBC group to 1.2% in the non-ALBC group as significant [10]. Statistical analyses were performed with JMP Pro 11.0 (SAS Institute, Cary, NC). A p-value of < 0.05 was considered significant. A logistic regression analysis followed by stepwise regression was performed to evaluate the preventive effect of ALBC, after adjusting for confounding factors. For measures, significance of categorical variables was determined with Fisher's exact test, and continuous variables were analyzed using the Student's *t*-test.

Results

The patients in the non-ALBC group were older and had a higher incidence of DM than those in the ALBC group, but, for each of the other four demographic variables, the difference between the patients in the two groups was not significant (Table 1).

The overall rate of deep SSI was 0.97% (11 of 1,138 patients) (Table 2). All of the infections occurred within three postoperative months. Except for two culture-negative cases, the organisms were multi-drug resistant (specifically, MRCNS (methicillin-resistant coagulase negative *Staphylococcus*) and MRSA (methicillin-resistant *Staphylococcus aureus*)).

There were eight deep SSIs in the ALBC group (rate: 1.4%) and three in the non-ALBC group (rate: 0.5%) (Table 3), with the difference not being significant ($p = 0.10$). Furthermore, the type of surgery did not significantly affect the rate of deep SSI in the comparison between the two study groups (Table 3). Results of the multivariate analysis show that the only significant variable is DM (Table 4). This was confirmed by the results of the stepwise regression after multivariate analysis (Table 5). The difference in incidence of deep SSI between patients with DM in the two study groups was not significant (Table 6), showing lack of efficacy of ALBC in this sub-set.

Discussion

Deep SSIs following arthroplasty must cause huge burdens on both patients and surgeons [1]. Surgeons

usually adopt every method to prevent SSIs including some adjunctive ones. Prophylactic administration of ALBC in cemented primary arthroplasties is widely used in many countries, such as the United Kingdom [6], Norway [7,8], and Sweden [9]. While a number of meta-analyses [5,10] and RCTs [18,19] showed the efficacy of ALBC, several reports showed no significant decrease in the incidence of infection with or without ALBC [11,12,20]. The purpose of the current study was to provide clinical data to a controversy on this issue.

The results of the present study showed that the use of ALBC did not reduce the occurrence of deep SSI after any type of primary arthroplasty, with the rate of deep SSI being 0.97% overall, 1.4% in the ALBC group, and 0.5% in the non-ALBC group. These rates were within the range of those obtained in the study by Garvin and Konigsberg on TKA (0.4% to 2%) [21]. The concept of using ALBC as a prophylactic method to reduce the occurrence of deep SSI has been largely based on the clinical experience obtained over the past three decades [10], however, it is not strongly supported by the basic experimental data as Parvizi declared in the article. Chang, et al. [22] concluded in their basic experimental report that gentamicin-loaded ALBC may be a very effective choice, but they also showed dramatic decrease in daily release during the first 14 days. Van de Belt, et al. [14] also concluded that ALBC does not necessarily inhibit the formation of an infectious biofilm because of rapid decrease of gentamicin release in their basic research. Although ALBC is appropriate for local drug delivery in cemented arthroplasty, the rapid decrease of drug release is supposed to be the reason of the results of the present study.

The opinion which supports ALBC in primary cemented arthroplasty was based on a number of RCTs and meta-analyses. Using Norwegian Arthroplasty Registry data, Espehaug, et al. [7] and Engesaeter, et al. [8] showed that systemic antibiotics combined with ALBC led to fewer revisions than other methods, such as systemic only or ALBC only. Josefsson, et al. [19] reported the results of an RCT with 1,688 THA cases and concluded that five-year follow-up of these cases clearly showed the prophylactic value of ALBC against deep infection. Chiu, et al. [23] also conducted a prospective randomized study of 340 primary TKA cases and showed effectiveness of cefuroxime-impregnated cement in the prevention of early to intermediate deep infection after surgery. Meta-analyses by Parvizi, et al. [10] and by Wang, et al. [5] demonstrated the effectiveness of ALBC with a large number of THA and TKA cases, respectively. However, some of these reports showed relatively higher occurrence rate of infection in "non-ALBC" cohort. For example, in the RCT by Chiu, et al. [23], deep infection developed in 3.1% of "without cefuroxime cement" group. In the meta-analysis by Parvizi, et al. [10], the rate of deep infection was 2.3% when cement without antibiotics was used. These "higher" infection rates might reach statistical significance in these studies. And from this point of view, lower overall infection rate might make it hard to reach statistical significance in the present study even though 1,138 cases had been recruited. Similarly, other reports which could not find significant difference with or without ALBC showed lower occurrence rate of deep infection, specifically, lower than 1.5% in the report by McQueen, et al. [11], Hinarejos, et al. [12], and Zeng, et al. [20].

The present study has two limitations. First, because of the relatively low rate of infection, the sample size may be susceptible to type II statistical error. Considering such low rates of infection, the study was underpowered to demonstrate a significant difference. It would have been necessary to have enrolled at least 2,200 patients in each treatment groups. These numbers are large enough that a clinical trial is unlikely to occur; therefore, a meta-analysis might be an appropriate way to resolve this problem. Second, because of the retrospective nature of the study, it was not possible to account for all potential confounding factors that might influence the rate of deep SSIs.

Some authors are against the routine use of ALBC for primary arthroplasty as infection prophylaxis because of its potential disadvantages. Thus, Hanssen [24] concluded that concerns about emerging drug-resistant organisms probably outweigh routine use of ALBC in all uncomplicated primary arthroplasties. The use of ALBC increases surgical cost [16,17], but it would be warranted if it could decrease the cost of an arthroplasty that might be increased by the revision surgeries caused by deep SSIs. Although several authors have analyzed the cost-effectiveness of ALBC, it remains controversial [1,25]. In addition to these concerns, the fact that several reports [11,12,20,26], including the present study, showed no significant decrease in infection rate seemed to indicate the validity of the Food and Drug Administration (FDA), that is, ALBC should not be used in primary cemented arthroplasty as an adjunctive prophylactic method.

In conclusion, ALBC did not significantly reduce the rate of deep SSIs in primary cemented arthroplasty as an adjunctive method. Similar trends were observed in the cohort with DM. A large, multi-center, cohort study might be needed to reach a firm conclusion regarding the efficacy of the adjunctive prophylactic use of ALBC after primary cemented arthroplasty.

Declarations

Ethics approval and consent to participate.

The Committee for the Ethics of Human Research of Hakodate Central General Hospital approved the study protocol, and informed consent was obtained from each of the patients whose records were included in the study.

Consent to Publish

Not applicable.

Competing Interests

The authors declare that we have no competing interests.

Authors' Contributions

FS and FO designed the study. FS, FO and MK performed the study, collected the data, and contributed to the study design. FS and DT prepared the manuscript. FS, MK and NI edited the manuscript. All authors read and approved the final manuscript.

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