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WJO covers topics concerning arthroscopy, evidence-based medicine, epidemiology, nursing, sports medicine, therapy of bone and spinal diseases, bone trauma, osteoarthritis, bone tumors and osteoporosis, minimally invasive therapy, diagnostic imaging. Priority publication will be given to articles concerning diagnosis and treatment of orthopedic diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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Antibiotic bone cement's effect on infection rates in primary and revision total knee arthroplasties

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Abstract

AIM

To compare infection rates in primary and revision total knee arthroplasty (TKA) procedures using antibiotic impregnated bone cement (AIBC) to those rates in procedures not using AIBC.

METHODS

A systematic review and meta-analysis was conducted in search for randomized controlled trials/studies (RCTs) pertaining to the field of antibiotic AIBC *vs* non-AIBC groups in both primary and revision TKA procedures. The primary literature search performed was to identify all RCTs that assessed AIBC in primary and revision TKA procedures. This search was done strictly through the PubMed database using the article "filters" setting that identified and separated all RCTs from the overall search. The original search was "Primary/revision total knee arthroplasty using AIBC". Other key terms and phrases were included in the search as well. Eligible articles that were used in the "results" of this review met the following criteria: (1) Involved primary or revision TKA procedures (for any reason); (2) included TKA outcome infection rate information; (3) analyzed an AIBC group *vs* a non-AIBC control group; (4) were found through the RCT filter or hand search in PubMed; and (5) published 1985-2017. Exclusion criteria was as follows: (1) Patients that were not undergoing primary or revision TKA procedures; (2) articles that did not separate total hip arthroplasty (THA) *vs* TKA results if both hip and knee revisions were evaluated; (3) papers that did not follow up on clinical outcomes of the procedure; (4) extrapolation of data was not possible given published results; (5) knee revisions not done on human patients; (6) studies that were strictly done on THAs; (7) articles that were not found through the RCT filter or through hand search in PubMed; (8) articles that did not evaluate AIBC used in a prosthesis or a spacer during revision; (9) articles that did not compare an AIBC group *vs* a non-AIBC control group; and (10) articles that were published before 1985.

RESULTS

In total, 11 articles were deemed eligible for this analysis. Nine of the 11 studies dealt with primary TKA procedures comparing AIBC to non-AIBC treatment. The other two studies dealt with revision TKA procedures that compared such groups. From these papers, 4092 TKA procedures were found. 3903 of these were primary TKAs, while 189 were revision TKAs. Of the 3903 primary TKAs, 1979 of these used some form of AIBC while 1924 were part of a non-AIBC control group. Of the 189 revision TKAs, 96 of these used some form of AIBC while 93 were part of a non-AIBC control group. Average follow-up times of 47.2 mo and 62.5 mo were found in primary and revision groups respectively. A two-tailed Fisher's exact test was done to check if infection rates differed significantly between the groups. In the primary TKA group, a statistically significant difference between AIBC and non-AIBC groups was not found (AIBC infection rate = 23/1979, non-AIBC infection rate = 35/1924, $P = 0.1132$). In the revision TKA group, a statistically significant difference between the groups was found (AIBC infection rate = 0/96, non-AIBC infection rate = 7/93, $P = 0.0062$). No statistically significant differences existed in Knee Society Scores, Hospital for Special Surgery Scores, or Loosening Rates.

CONCLUSION

AIBC did not have a significant effect on primary TKA infection rates. AIBC did have a significant effect on revision TKA infection rates.

Key words: Total knee arthroplasty; Knee revision; Antibiotic impregnated/laden/infused bone cement; Bone cement; Knee arthroplasty; Primary/revision total knee arthroplasties infection

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Core tip: A systematic review and meta-analysis of randomized controlled trials/studies on primary and revision total knee arthroplasties (TKA) using antibiotic impregnated bone cement (AIBC). AIBC was found to lower infection rates in revision TKA procedures, but not in primary TKA procedures.

Kleppel D, Stirton J, Liu J, Ebraheim NA. Antibiotic bone cement's effect on infection rates in primary and revision total knee arthroplasties. *World J Orthop* 2017; 8(12): 946-955 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i12/946.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i12.946>

INTRODUCTION

The use of antibiotic impregnated bone cement (AIBC) was first described by Buchholz and Englebrecht^[1] in 1970. Throughout the years since, AIBC's mechanical properties and use in a clinical setting have been expounded upon greatly. In as early as 1981, Buchholz

et al^[2] reported up to a 77% success rate using AIBC, many times without systemic antibiotics, in primary total hip arthroplasty (THA) and total knee arthroplasty (TKA) procedures. More recently, antibiotic infused spacers have also been described in two stage joint knee revision procedures to reduce the rate of infection during and after revision.

Since AIBC was first introduced into the field of orthopedics there has been controversy over its safety and how antibiotics affect the bone cement. In addition to the problem of organism specific antibiotic resistance, mechanical loosening may also result from antibiotic combination. One study^[3] found that in low doses (≤ 2 g of antibiotic powder per 40 g cement) AIBC does not lead to an increased rate of mechanical loosening. However, other studies^[3-5] have indicated that in much higher doses (> 4.5 g of antibiotic powder per 40 g cement) or with usage of liquefied antibiotics in bone cement, mechanical problems such as loosening in the prosthesis can occur more frequently. Adalberth *et al*^[6] performed a study demonstrating that antibiotics added to bone cements had similar fixation, extent of radiolucent lines, and clinical outcomes as compared to plain bone cement (PBC). Moreover, in a recent systematic review and meta-analysis published in 2013 inspecting eight randomized controlled trials/studies (RCTs) comparing AIBC and non-AIBC primary TKA and THA procedures, there was shown to be no difference in rate of aseptic loosening when antibiotics were added to the cement as compared to the control^[7].

Much of the information published and reviewed on antibiotic and antiseptic usage thus far has focused on primary total joint arthroplasty (TJA) procedures. Nevertheless, promise has been shown using AIBC in revision procedures. Clinically, AIBC is widely accepted to cure surgical site infections during revision procedures^[8,9]. Peersman *et al*^[10] noted that rates of infection following revisions are approximately 2-3 times higher than rates following primary procedures. In 2015, Bini *et al*^[11] published that AIBC used in revision TKA procedures nearly halved the risk of re-revision suggesting AIBC's potentially crucial role in infection prevention during revision procedures. Furthermore, the planet is experiencing a large increase in elderly populations, which will most likely increase the need for TKA procedures in the near future. Kurtz *et al*^[12] demonstrated that with this increase in age, there will also be an increase in deep infection rates following primary TKA. These rates are expected to rise up to 6.8% within the next 15 years. These statistics portray how important AIBC will be in the future of both primary and revision TKA procedures.

In recent years, the use of prophylactic antibiotics and antiseptics in both primary and revision TJA have been explored through systematic reviews found on PubMed^[7,13-15]. Although interest in the area of antibiotics and antiseptics on infection rates in both primary and revision TKA and THA procedures has increased, there has been a lack of high quality information published in systematic reviews to draw relevant conclusions

from^[13].

Not only has there been a shortage of studies that have explored this field, but many of the studies done have shown variable and inconclusive data. In a more detailed look at these studies, there was one systematic review that analyzed over 6300 primary TKAs and THAs that showed no statistically significant differences in the rates of deep infection or superficial infection between the group that used AIBC and the group that used PBC^[7]. Similar results were found in two other systematic reviews published in 2015 and 2016 as well^[14,15]. However, these studies did not include the most up-to-date articles on primary and revision TKA procedures. These reviews were not limited to RCTs and therefore did not consider the most credible sources for data collection in the field. Past reviews have not included information on TKA revisions, which is an overly unexplored field that will be considered in this systematic review.

The inconsistencies in search criteria and evaluations reported in most of these studies reveal the importance of a systematic review and meta-analysis on this topic. As shown from the search conducted on this topic in PubMed, there has not been an up-to-date systematic review evaluating both primary and revision TKA procedures with AIBC vs non-AIBC control groups strictly in randomized controlled trials/studies in the current literature. As agreed upon in multiple studies^[16,17], periprosthetic joint infections are some of the most devastating complications of TKA procedures and the importance of their prevention is of great value to the field of orthopedics. It is hypothesized that AIBC will result in lower infection rates amongst primary and revision TKA procedures. Therefore, the purpose of this review and analysis was to combine the most up-to-date and relevant data from RCTs focusing on primary and revision TKA procedures using AIBC vs not using AIBC. This study aimed to primarily analyze and compare infection rates in primary and revision AIBC procedures to those rates in procedures not using AIBC. A secondary aim was to examine other clinically significant differences between groups using and not using AIBC during primary and revision TKAs.

MATERIALS AND METHODS

Study design

A systematic review and meta-analysis was conducted in search for randomized controlled trials/studies (RCTs) pertaining to the field of AIBC vs non-AIBC groups in both primary and revision total knee arthroplasty procedures.

Literature search

The primary literature search performed was to identify all randomized controlled trials/studies that assessed antibiotic impregnated bone cement in primary and revision TKA procedures. This search was done strictly through the PubMed database using the article "filters" setting that identified and separated all RCTs from the

overall search. The original search was "Primary/revision total knee arthroplasty using AIBC".

Other key terms and phrases in the search included "primary TKA infection", "primary knee infection", "knee revision infection", "knee revision failure", "revision TKA infection", "antibiotic impregnated/ laden/ infused bone cement", "2 stage knee revision", and "1 stage knee revision". In addition, search terms such as "gentamicin", "tobramycin", "cefuroxime", "cefazolin", and "vancomycin" were used in conjunction with the phrases above. After the primary literature search was conducted, articles that met relevant criteria were further scanned in their titles and abstracts for inclusion. Once articles' titles and abstracts were scanned, the articles were hand-searched for other sources that could be of relevance to the topic. PubMed articles that did not initially show full text access were searched in Ovid, MEDLINE database as well as in the Journal of Bone and Joint Surgery (American volume), and Clinical Orthopedics and Related Research. During the screening process all titles and abstracts were inspected for the key search terms mentioned. This search was conducted up until July 2017.

Inclusion and exclusion criteria

Eligible articles that were used in the "results" of this review met the following criteria: (1) Involved primary or revision TKA procedures (for any reason); (2) included TKA outcome infection rate information; (3) analyzed an AIBC group vs a non-AIBC control group (4) were found through the RCT filter or hand search in PubMed; and (5) published 1985-2017.

Exclusion criteria was as follows: (1) Patients that were not undergoing primary or revision TKA procedures; (2) articles that did not separate THA vs TKA results if both hip and knee revisions were evaluated; (3) papers that did not follow up on clinical outcomes of the procedure; (4) extrapolation of data was not possible given published results; (5) knee revisions not done on human patients; (6) studies that were strictly done on THAs; (7) articles that were not found through the RCT filter or through hand search in PubMed; (8) articles that did not evaluate AIBC used in a prosthesis or a spacer during revision; (9) articles that did not compare an AIBC group vs a non-AIBC control group; and (10) articles that were published before 1985.

Exclusion criteria were limited to studies evaluated in the results of this paper. Multiple studies were used as references in this paper that did not meet the inclusion criteria or that did meet the exclusion criteria. However, these articles were used only in the introduction and discussion sections of this review to bring other relevant data on this topic into light. It is important to note that data from these articles may still be relevant to the topic, but do not meet inclusion criteria for analysis in this paper. Inclusion criteria were selected in order to set a standard for comparison amongst the RCTs discovered upon the systematic search. If study information was unclear, authors were contacted requesting the relevant

Table 1 Data from primary total knee arthroplasty randomized controlled trials

Paper	AIBC group number of TKAs infected	Infection rate of AIBC group	Non-AIBC number of TKAs infected	Infection rate of non-AIBC group	Reason for procedure	Follow-up (mo)
Chiu <i>et al</i> ^[18] , 2001	0/41	0	5/37	0.13514	Osteoarthritis	50
Vrabec <i>et al</i> ^[23] , 2016	0/10	0	0/5	0	N/A	12
Chiu <i>et al</i> ^[19] , 2002	0/178	0	5/162	0.03086	N/A	49
Lizaur-Utrilla <i>et al</i> ^[24] , 2014	1/48	0.020833	0/45	0	Non-inflammatory arthritis	76.8
Nilsson <i>et al</i> ^[25] , 1999	0/28	0	2/29	0.068966	Osteoarthritis and Rheumatoid arthritis	60
Bercovy <i>et al</i> ^[26] , 2012	2/164	0.012195	1/157	0.006369	N/A	91.2
Hinarejos <i>et al</i> ^[20] , 2013	20/1483	0.013486	20/1465	0.013652	N/A	38
McQueen <i>et al</i> ^[22] , 1987	0/13	0	1/13	0.076923	Osteoarthritis and rheumatoid arthritis	24
McQueen <i>et al</i> ^[21] , 1990	0/14	0	1/11	0.090909	Osteoarthritis	24
Total: 23/1979 (1.16%)			Total: 35/1924 (1.82%)			Average: 47.2

AIBC: Antibiotic impregnated bone cement; TKA: Total knee arthroplasty.

information to check eligibility of the article.

Outcome measures

The chief outcome evaluated in this analysis was infection rate following primary or revision TKA. Other factors were assessed and quantified including follow-up times, record of previous infection, whether or not systemic antibiotics were used to supplement AIBC, and publication year. Variables reported in more than one paper that were noted in this analysis included whether or not there was a statistically significant difference in deep infection rates, loosening rates, Knee Society Scores (KSS), and Hospital for Special Surgery Scores (HSS).

Article quality

Only randomized controlled trials were assessed. Articles were published in reputable journals including the Journal of Bone and Joint Surgery, Journal of Arthroplasty, Journal of Clinical Orthopaedics and Related Research, Journal of International Orthopaedics, and the Journal of Knee Surgery, Sports Traumatology, and Arthroscopy. All articles were deemed of high quality based on these factors.

Literature search results

After searching all key terms and phrases, a total of 176 RCTs were shown on the PubMed database. After initial screening of titles and abstracts, 148 articles were eliminated because they were deemed irrelevant to this study for various reasons (Figure 1). The 28 remaining articles were full-text hand searched in order to identify if they were appropriate for this study. Of the 28 articles, six were found to fit inclusion criteria. Five more articles were also found to fit inclusion criteria through the full-text hand search of the 28 articles. Therefore, 11 articles in total were found in the initial screening and secondary hand search. Further details of this search and screening procedure using inclusion and exclusion criteria were found in a flow chart (Figure 1). Further information from the articles including first author, year published, number of TKAs studied, infection rates, follow-up times, and reason for the TKA

procedures was noted in Tables 1 and 2. RCTs' individual comparisons were shown in Tables 3 and 4. Information on loosening rates, statistically significant differences in deep infection found in individual articles, and KSS and HSS knee scores were described in Table 5.

Statistical analysis

From the studies searched, important statistics were extracted and compiled into Excel documents for analysis. Averages and totals were calculated for relevant data sets as mentioned in the "outcome measures" section above. A two-tailed Fisher's exact test was used to calculate statistically significant differences in infection rates between groups. Differences in loosening rates were calculated using a two-tailed Fisher's exact test as well. Differences in KSS/HSS knee scores were calculated using a two-tailed, type-3 *t*-test (95%CI).

RESULTS

General study characteristics

In total, 11 articles were deemed eligible for this analysis. Nine of the 11 studies dealt with primary TKA procedures comparing AIBC to non-AIBC treatment^[18-26]. The other two studies dealt with revision TKA procedures that compared such groups^[17,27]. From these papers, 4092 TKA procedures were found. 3903 of these were primary TKAs, while 189 were revision TKAs. Of the 3903 primary TKAs, 1979 of these used some form of AIBC while 1924 were part of a non-AIBC control group. Of the 189 revision TKAs, 96 of these used some form of AIBC while 93 were part of a non-AIBC control group. Average follow-up times of 47.2 mo and 62.5 mo were found in primary and revision groups respectively. In six of the studies, the TKA procedures were conducted after a diagnosis of some form of arthritis^[17,18,21,22,24,25]. In one study^[27], the revision TKAs were done because of previous infection. Four of the studies did not report such data on the patient population used^[19,20,23,26]. In all of the studies, systemic antibiotics were used in conjunction with AIBC to facilitate recovery and prevent reinfection.

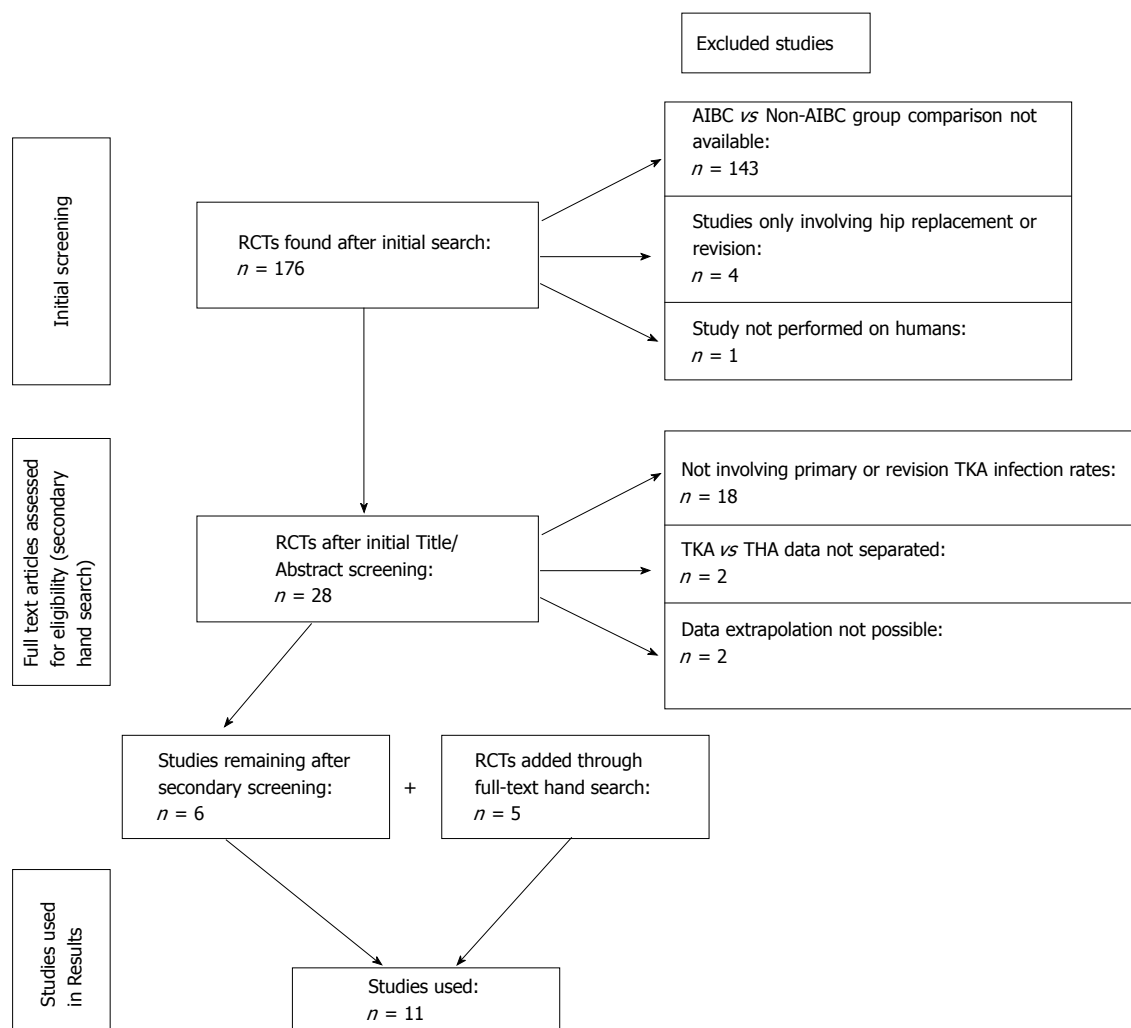


Figure 1 Flow diagram for studies included in result analysis. This flow chart describes the articles that were included and excluded in the analysis based on the initial screening and further full-text assessment. Articles that were assessed and screened are shown to the left. Articles that were excluded are shown to the right. Right pointing arrows lead to excluded articles in different parts of the screening and evaluation processes. Downward pointing arrows show points from one set of screenings to the next, displaying how many articles were left after exclusion criteria had been considered. Reasons for exclusion were also shown in the right column. AIBC: Antibiotic impregnated bone cement; TKA: Total knee arthroplasty; THA: Total hip arthroplasty; RCTs: Randomized controlled trials /studies.

Table 2 Data from revision TKA RCTs

Paper	AIBC group number of TKAs infected	Infection rate of AIBC group	Non-AIBC number of TKAs infected	Infection rate of non-AIBC group	Reason for procedure	Follow-up (mo)
Nelson <i>et al</i> ^[27] , 1993	0/3	0	0/3	0	Previous infection	36
Chiu <i>et al</i> ^[17] , 2009	0/93	0	7/90	7.78%	Osteoarthritis	89
	Total: 0/96 (0.00%)		Total: 7/93 (7.53%)			Average: 62.5

RCTs: Randomized controlled trials/studies; AIBC: Antibiotic impregnated bone cement; TKA: Total knee arthroplasty.

Also, eight of the 11 studies had an infection rate of 0.0% when AIBC was used, even with an average follow up of over 47 mo amongst those studies. However, only three of the 11 studies found a 0.0% infection rate when AIBC was not used. These differences were not large enough in the primary TKA group to indicate statistical significance, but did indicate AIBCs crucial role in preventing infection post-revision. Overall, AIBC groups were compared to PBC groups, systemic antibiotic groups, and hydroxyapatite coated prostheses groups. All studies used in the results/analysis were published

between 1987-2016 with an average publication year of 2003.

Infection rates

A two-tailed Fisher's exact test was done to check if infection rates differed significantly between the groups. Deep infection rates were analyzed in this review because superficial infection rates were not reported to be statistically significant in any of the articles. In the primary TKA group, a statistically significant difference between AIBC and non-AIBC groups' infection rates

Table 3 Comparisons made between groups in primary TKA RCTs

Paper	Comparison
Chiu <i>et al</i> ^[18] , 2001	Cefuroxime-impregnated cement <i>vs</i> PBC
Vrabec <i>et al</i> ^[23] , 2016	Intravenous tobramycin <i>vs</i> AIBC with tobramycin
Chiu <i>et al</i> ^[19] , 2002	Cefuroxime-impregnated cement <i>vs</i> PBC
Lizaur-Utrilla <i>et al</i> ^[24] , 2014	Tibial fixation with either a cemented (Palacos with Gentamicin) <i>vs</i> cementless with screw augmentation (systemic antibiotics only)
Nilsson <i>et al</i> ^[25] , 1999	Vacuum mixed bone cement (Palacos-Gentamicin) <i>vs</i> hydroxyapatite-coated prostheses
Bercovy <i>et al</i> ^[26] , 2012	Hydroxyapatite-coated prostheses <i>vs</i> cemented (Refobacin) tibial components
Hinarejos <i>et al</i> ^[20] , 2013	Simplex P cement loaded with 0.5 g of erythromycin and three million units of colistin in 40 g of cement (Stryker) <i>vs</i> simplex cement without antibiotic
McQueen <i>et al</i> ^[22] , 1987	Cefuroxime in bone cement (1.5 g of cefuroxime powder was added to 40 g of CMW cement powder) <i>vs</i> systemic (1.5 g) cefuroxime
McQueen <i>et al</i> ^[21] , 1990	Cefuroxime in bone cement (1.5 g of cefuroxime powder was added to 40 g of CMW cement powder) <i>vs</i> systemic (1.5 g) cefuroxime

CMW: A kind of bone cement made by CMW laboratories of DePuy Synthes Companies; RCTs: Randomized controlled trials/studies; PBC: Plain bone cement; AIBC: Antibiotic impregnated bone cement.

Table 4 Comparisons made between groups in revision TKA RCTs

Paper	Comparison
Nelson <i>et al</i> ^[27] , 1993	Gentamicin-PMMA beads <i>vs</i> conventional systemic antibiotics
Chiu <i>et al</i> ^[17] , 2009	AIBC (vancomycin-impregnated) <i>vs</i> PBC in TKA Revision

RCTs: Randomized controlled trials/studies; PMMA: Polymethyl methacrylate; AIBC: Antibiotic impregnated bone cement; TKA: Total knee arthroplasty; PBC: Plain bone cement.

was not found (AIBC infection rate = 23/1979, non-AIBC infection rate = 35/1924, $P = 0.1132$). In the revision TKA group, a statistically significant difference between the groups' infection rates was found (AIBC infection rate = 0/96, non-AIBC infection rate = 7/93, $P = 0.0062$). AIBC used directly in the revision prosthesis benefitted patients and helped prevent infection. Further information for individual articles having to do with the items mentioned in this paragraph was noted in Tables 1 and 2.

Other quantifiable variables reported

Other variables reported in more than one study were loosening rates^[17,18,24,26,29], postoperative KSS scores^[24-26], and postoperative HSS scores^[17-19]. Loosening rates did not significantly differ between groups ($P = 1.00$). Postoperative HSS and KSS scores also did not differ significantly between groups ($P = 0.1208$ and $P = 0.38496$ respectively). Tables 1 and 2 reported numbers of TKA procedures and rates of infection for each paper. Table 5 supplied additional information on loosening rates and KSS/HSS scores.

In all studies that reported superficial infection rates, there were no statistically significant differences between AIBC and non-AIBC groups. Superficial infection rates were almost always higher than deep infection rates in both groups. Three papers reported having statistical significance when comparing deep

infection rates amongst groups^[17-19]. More than half of the studies reported deep infections to occur in an early to moderate time period after the operation, while none of the studies reported chronic deep infection to be the most common type of infection after procedures.

Significant results from individual papers

Vrabec *et al*^[23] described that local concentrations of antibiotics from AIBC not only had supratherapeutic concentrations in the joint fluid, but also achieved therapeutic concentrations locally within the first 48 h postoperatively. Systemic antibiotics, on the other hand, only achieved subtherapeutic levels locally, not in the joint fluid.

In Lizaur-Utrilla *et al*^[24], statistically significant differences were found in clinical outcomes such as knee score ($P = 0.022$), range of motion ($P = 0.042$), and WOMAC ($P = 0.036$) between groups, all favoring cementless components. Lizaur-Utrilla *et al*^[24] also reported that cementless TKA was the better option for younger patients with osteoarthritis even though revision rates and survival rates were similar between cemented and cementless groups.

Results from three different studies found *Staphylococcus aureus*, *Staphylococcus epidermidis*, coagulase-negative *Staphylococcus*, and group-B *Streptococcus* to be the most common organisms found in TKA deep infection cultures^[17,18,21]. Also, Chiu *et al*^[17] reported that those organisms identified through culture in revision infections are more virulent and less sensitive to certain cephalosporin antibiotics than those found in primary TKA infections.

All studies done by Chiu *et al*^[17-19] were conducted in a country outside of the United States, where operating room standards are unequivocal to more medically advanced nations. Their results were therefore most relevant for TKAs performed in an operative setting lacking "clean-air measures" such as ultraviolet light, laminar flow, and body exhaust systems. Chiu *et al*^[18] 2001 and Chiu *et al*^[17] 2009 reported that adding certain antibiotics such as cefuroxime or vancomycin only cost

Table 5 HSS, KSS knee scores, and loosening rates

Paper	Statistically significant differences in deep infection rate	HSS knee score AIBC	HSS knee score non-AIBC	KSS score AIBC	KSS score non-AIBC	Loosening AIBC	Loosening non-AIBC
Chiu <i>et al</i> ^[18] , 2001	Yes ($P = 0.021$)	91	86	-	-	0/41	2/37
Vrabec <i>et al</i> ^[23] , 2016	No (P value not reported)	-	-	-	-	-	-
Chiu <i>et al</i> ^[19] , 2002	Yes ($P = 0.0238$)	90	88	-	-	1/178	0/162
Lizaur-Utrilla <i>et al</i> ^[24] , 2014	No (P value not reported)	-	-	89	94	4/48	1/45
Nilsson <i>et al</i> ^[25] , 1999	No (P value not reported)	-	-	93	93	0/28	1/29
Bercovy <i>et al</i> ^[26] , 2012	No (P value not reported)	-	-	94.3	94.6	1/164	1/157
Hinarejos <i>et al</i> ^[20] , 2013	No ($P = 0.96$)	-	-	-	-	-	-
McQueen <i>et al</i> ^[22] , 1987	No (P value not reported)	-	-	-	-	-	-
McQueen <i>et al</i> ^[21] , 1990	No (P value not reported)	-	-	-	-	-	-
Nelson <i>et al</i> ^[27] , 1993	No (P value not reported)	-	-	-	-	-	-
Chiu <i>et al</i> ^[17] , 2009	Yes ($P = 0.0130$)	87	85	-	-	0/93	0/90

AIBC: Antibiotic impregnated bone cement; HSS: Hospital for special surgery scores; KSS: Knee society scores.

\$ 10-15 in Taiwan, where their studies were conducted. The price for adding antibiotics to bone cement was reported to cost much less than having to do a possible re-revision due to infection if antibiotics were not added to the cement. Chiu *et al*^[18] 2001, Chiu *et al*^[17] 2009, and Hinarejos *et al*^[20] 2013 considered other factors that could correlate with the development of infection such as age, sex, side of the lesion, reason for the revision, time between the primary and revision procedures, body mass index, ASA grade, tourniquet time, operative time, hospital stay, HSS score, and period of follow-up. None of these factors were significant in the development of infections in any of these studies.

Hinarejos *et al*^[20] did not report erythromycin and colistin-loaded cements to significantly impact infection rates in primary TKAs. In Hinarejos *et al*^[20] study, there was an average operation time 4.4 min longer in the group with an infection and the group with deep infections had significantly higher percentages of procedures over 125 min. With this data, Hinarejos *et al*^[20] found that male sex and an operating time of > 125 min were factors related to a higher rate of deep infection.

McQueen *et al*^[22] 1987 detailed that the knee arthroplasty that had been diagnosed with a deep infection in the group not using AIBC had previously undergone a medial meniscectomy and a proximal tibial osteotomy, which accounted for higher chances of infection following that operation.

When looking at hydroxyapatite (HA) coating vs cemented TKA components, Nilsson *et al*^[25] and Bercovy *et al*^[26] both found that HA-coated implants were more stable than cemented implants. Bercovy *et al*^[26] noted that HA-coated components performed similarly to cemented components and both Bercovy *et al*^[26] and Nilsson *et al*^[25] reported HA-coated implants to be a reliable option in primary TKA procedures. Other various elements were described in all of the studies, however, only the most frequent were reported in this analysis. More information on comparison details from individual articles was noted in Tables 3 and 4.

Bone cements and antibiotics

Different types of antibiotics added to bone cements

involved in this analysis included cefuroxime, vancomycin, tobramycin, gentamicin, rifobacin, colistin, and erythromycin. Cefuroxime and vancomycin were the antibiotics used in studies with significant differences in infection rates. More information about types and amounts of bone cements/antibiotics used in these papers was presented in Tables 3 and 4.

DISCUSSION

Overall analysis displayed AIBC's potential as an infection prevention tool. It was found that the use of AIBC did not reduce the infection rates in primary TKAs. A possible explanation for this insignificant difference could be that primary TKA procedures are 2-3 times less susceptible to infection^[10] than TKA revisions, making AIBC less relevant in the prevention of infection outcomes in primary vs revision TKA procedures. In primary TKA procedures, both AIBC and other forms of systemic antibiotics have been proven to be equally effective in infection prevention^[7]. However, the opposite is true for revision TKA. With revision TKAs, the only outcome found to vary significantly between AIBC and non-AIBC groups was infection rates. Since revision TKAs have higher chances of infection and are oftentimes undergone because of previous infection, the added benefits of AIBC during the revision procedure could significantly decrease infection post-revision. With this data, the hypothesis that AIBC would lower infection rates in TKA revisions was supported. The hypothesis that AIBC would lower infection rates in primary TKAs was not supported.

Some individual papers noted significant differences between groups in multiple ways, but with the strict inclusion criteria used in this paper, perhaps not enough papers were included to obtain significant results for variables besides infection rates. There were no differences in clinical knee scores found in this study or in the systematic review done by Wang *et al*^[7]. None of the studies noted differences in superficial infection rates. Josefsson *et al*^[28] proposed that the antibiotics from loaded cement do not reach the superficial parts of the wound in a sufficient concentration to prevent infection. This gave one explanation for the lack of

statistical significance in superficial infection rates found throughout literature reviews as well^[7,13-15].

This systematic review differed from other systematic reviews in multiple ways. The systematic review and meta-analysis done previously on primary TKA and THA AIBC vs non-AIBC groups was published in 2013^[7]. That systematic review had articles published up until 2013 and used four RCTs^[19-22] that were used in this analysis paper. With the goal of including the most recent published results in the field, this study included two papers^[23,24] published after 2013. This study also included seven other RCTs that the previous meta-analysis^[7] did not (five extra primary TKA RCTs and two revision TKA RCTs). In that systematic review^[7], there were also no significant differences in infection rates in the TKA group found. Other reviews^[14,15] published with similar search criteria as Wang *et al.*^[7] found insignificant results as well. However, these reviews did not include similar search criteria and were not limited to RCTs only. None of these reviews considered TKA revisions.

Even though this study sought to include a large number of revision TKA procedures, there were a limited number of patients found that were evaluated in revision TKAs. As noted in the limitations section, this was a drawback to this study. If a larger sample size in the revision TKA group were possible, this data would be even more clinically significant. Without such additional data, conclusions would be hard to make, but considering data from this study it is speculated that revision TKA procedures would continue to show significant differences in AIBC vs non-AIBC infection rates.

Most studies suggest that both systemic antibiotics and AIBC be used when treating septic patients. In the results of this analysis, it was found that the use of systemic antibiotics in conjunction with AIBC was the standard in all 11 articles. One comprehensive literature review^[29] recommended that for best results prophylactic antibiotics be used before revision TKA, AIBC used during the procedure, and the surgery should also be followed with systemic antibiotics.

The primary advantage of preventing deep peri-prosthetic joint infection often outweighs the minor shortcoming of AIBC. According to Chiu *et al.*^[17], there is a significant cost benefit to adding antibiotics to bone cement. Chiu *et al.*^[17] stated that adding antibiotics to bone cement in revision procedures would cost much less than having a re-revision performed. The reality is that most surgical revisions use AIBC with antibiotics and bone cements in various combinations. It is evident that standards for safe use of AIBC must be followed for successful clinical results.

Even though the data suggests that AIBC significantly reduces the risk of infection in revision, there is clearly a shortage of high quality randomized controlled studies comparing AIBC to non-AIBC use in knee revision procedures. Furthermore, only two of the RCTs^[17,27] meeting criteria in the study had data comparing an AIBC group with a group not using AIBC during revision. This

could be explained by the strict inclusion and exclusion criteria set for this literature search. In the future, a literature search encompassing a more broad scope of papers that fit a different set of criteria could be done to get a larger sample size and more significant results from analysis. In order to have more significant results for AIBC in TKA procedures, more RCTs also need to be conducted with the specific aim of comparing AIBC use in TKA procedures vs procedures not using AIBC or some other form of antibiotic therapy. Although this study was limited to primary and revision TKAs, even more possibilities exist with AIBC in other joint reconstructive surgeries. With an increasing population, numbers of primary TKA and TKA revisions are bound to increase in the near future^[12]. The availability of potential patients needing TKA procedures that can be used in studies will therefore soon also be increasing. With this increase, hopefully more high quality studies and data can be accumulated on this topic.

Limitations

In spite of the fact that strong efforts were made to create a well-designed study, there were some intrinsic limitations in this review. One of the first limiting factors of note came about in the literature search. After some time searching for RCTs based through PubMed on this topic, it was clear that not many were available for use that met inclusion criteria. It was especially difficult to find RCTs that compared AIBC to a non-AIBC control in total knee revisions (only two studies found on this). Upon search, more articles were found pertaining to primary TKA/THA with AIBC. Revision procedures were seen to a much smaller extent. For these reasons, the sample size was relatively small and could potentially be expanded if studies outside of RCTs found using only the PubMed "filters" setting were included. Another limitation was that not all studies were held to the same standard of evaluation during patient follow up. Due to the fact that some studies were only focused on infection rates while others were focused on clinical knee scores and patient satisfaction, there was not a standard of comparison across each and every study evaluated. Along those same lines, knee scores were reported in two different ways (Knee Society Score and Hospital for Special Surgery Score), making them difficult to compare amongst papers. As expected, not all studies had the same follow up times, which made comparison between short, intermediate, and long term results more difficult. Also, not all revisions were done for the same purposes. Also, eligible studies came from hospitals located across many different countries, which have different populations of patients and populations of bacteria. Since we did not restrict our study to a certain type of bone cement or prostheses, many types of bone cements and implants were used across articles. All of these limitations may affect outcomes of this review and meta-analysis in some way.

AIBC did not have a significant effect on primary TKA infection rates. AIBC did have a significant effect on

revision TKA infection rates.

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