MAEDICA – a Journal of Clinical Medicine
2023; 18(2): 197-202
https://doi.org/10.26574/maedica.2023.18.2.197

MAEDICA - a Journal of Clinical Medicine

ORIGINAL PAPER

Effectiveness of Intra-Articular Injection of Ceftazidime/Vancomycin Combination during Total Knee Replacement: Prevention of Periprosthetic Joint Infection

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ABSTRACT

Background: *The occurrence of prosthetic joint infection (PJI) subsequent to total knee arthroplasty (TKA), also known as total knee replacement, is a highly detrimental complication. Some studies have concluded that intra-articular antibiotic injection was an effective approach to prevention of PJI, while others have reached the opposite conclusion. However, there is no study performed in one center, by one surgeon, one surgical team, or one type of prosthetic device.*

Methods: *This was a historical cohort study on patients who underwent primary TKA with vancomycin and ceftazidime (652 cases from September 2019 to the end of December 2020) and were compared with a cohort of patients also treated with TKA but without using antibiotic injection (620 controls from March 2018 to the end of August 2019). The incidence of PJI was followed for two years in each group by chart review.*

Results: *Study groups were matched for age (P-value 0.193), gender (P-value 0.913), body mass index (BMI) (P-value 0.136), and radiologic features of their knees (P-value > 0.05). Prosthetic joint infection was developed by only three patients: one (0.18%) in the case group and the remaining two (0.32%) in the control group (P-value 0.615); all three patients had a positive response to the treatment which included debridement, antibiotics, implant retention (DAIR) surgery and a course of antibiotics.*

Conclusion: *To our knowledge, this is the most precisely matched cohort of TKA subjects in this era. Intra-articular injection of vancomycin and ceftazidime during TKA showed no significant difference in reducing the risk of PJI in the case group. However, although PJI is a rare event in joint replacement surgery, it should be prospectively investigated in a study with even larger sample sizes.*

Keywords: prosthetic joint infection (PJI), total knee arthroplasty (TKA), ceftazidime, vancomycin.

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Article received on the 24th of May 2023 and accepted for publication on the 20th of June 2023

INTRODUCTION

Total knee arthroplasty is a surgical procedure that provides excellent results in pain relief and function restoration (1). Prosthetic joint infection is the third most common cause of TKA failure in developed countries (2). Postoperative deep wounds are a cause for significant concern, as infections in the surgical site can result in prolonged hospitalization, increased financial burden for the patient and elevated mortality rates (3). Prosthetic joint infection is one of the most dangerous complications of TKA surgery and the most important reason for the revision of TKA (4). Studies have shown that deep infections occur in 1.1% to 1.7% of TKA surgeries (5). Deep infection in TKA has serious effects on human health, which leads to bone destruction, degeneration of the replacement area and even death, so infection in these parts has been reported to range between 1-23% (6). The use of prophylactic antibiotics in general surgery of joint replacement is an effective strategy for reducing infection after surgery (7), so that more than 80% of infections in the surgical area with the correct prescription of prophylactic antibiotics would be reduced (8).

Intra-articular injection of vancomycin and ceftazidime in TKA is a controversial issue. Several authors supported its use because they believe might reduce the risk of infection (9-14), while others found that the administration of vancomycin and ceftazidime through intra-articular injection did not have a significant impact on infection risk reduction (15, 16). For this reason, in the literature there is no standardized way of injecting or not injecting this combination of antibiotics that is definitively beneficial or detrimental to the injection. However, to the best of our knowledge, most of the existing relevant studies with a large sample size were carried out in multiple centers and by different surgeons. But so far, no study with a relatively high sample size has been conducted in one center, by a single surgeon and one surgical team, with one type of prosthesis to examine the effect of intra-articular antibiotic injection in PJI prevention. Therefore, we designed an analysis to compare the outcomes after primary TJA between a group treated with an intra-articular injection of vancomycin and ceftazidime and a control group that did not receive any intra-wound antibiotics. The aimi of our study was to determine whether the application of intra-articular antibiotic could reduce the infection rate after primary total joint replacement. ❑

MATERIAL AND METHODS

This is a retrospective historical cohort study on non-traumatic and non-hemophilic patients eligible for TKA, who were operated on by a single orthopedic surgeon (M. Ayati Firoozabadi), in Mortaz hospital, Yazd, Iran, from March 2018 to December 2020. Exclusion criteria comprised medical history of knee fracture, hemophilic patients, medical history of femoral or tibial osteotomy, and subjects with known allergy to vancomycin or ceftazidime. Participants were placed into two groups: one receiving intra-articular injection of vancomycin/ceftazidime combination (the case group, 652 patients) and the other one not receiving the study medication (the control group, 620 patients). Furthermore, the mean duration of follow-up for the case and control groups was two years, during which the diagnosis of PJI was established in accordance with the criteria outlined during the PJI consensus meeting of 2018 (17).

By researching the TKA database, all patients with PJI who underwent two- or one-stage knee replacement surgery or DAIR for the treatment of PJI, perfomed by Dr. M. Ayati Firoozabadi from March 2018 to the present, were studied. All data were collected based on the review of archived patient medical records stored in Mortaz hospital. A comprehensive chart review was conducted to ensure that the diagnosis of PJI was based on culture results, sensitivities, antibiotic regimens, recurrence of infection, subsequent surgery and TKA status according to the infection at the time of the last clinical follow-up.

Ethical considerations

The research methodology was approved by Tehran University of Medical Science, Iran. As we conducted a retrospective chart review study, informed consent was obtained during the last follow-up and all personal patient data were unidentifiable. All controls received antibiotics after surgery to prevent surgical site infection.

Statistical analyses

The statistical software SPSS version 26 was utilized to conduct data analysis. Descriptive statis-

tics included mean and standard deviation (SD) for quantitative variables, and frequency and percentage for qualitative variables. In the inferential statistics section, chi-square and Fisher's exact tests were utilized to examine the relationship between qualitative variables, while two-sample independent t-tests were used to compare quantitative variables between the two groups. A significance level of 0.05 was employed for all tests. ❑

RESULTS

Of all study participants, 85.5% were females and 14.5% males. The results of descriptive statistics showed that patients had an average age of 65.39±8.04 years, an average weight of 76.70±12.31 kg, an average height of 167.58±6.53 cm and an average BMI of 27.17±3.25. Independent t-test showed that the average difference in age between the case and

TABLE 1. Demographic and radiographic variables study groups

Variables		Control group	Case group	P-value
Age, mean years ± SD		65.35 ±8.02	65.56 ±8.07	0.139
Female to male ratio		5.97	5.86	0.913
BMI, mean ± SD		27.31 ±3.51	27.04 ±2.98	0.136
Varus knee deformity, mean degree ± SD	IMA	6.21 ±1.08	6.24 ±1.07	0.746
	LDFA	91.28 ±3.68	91.33 ±3.66	0.145
	MPTA	86.71 ±3.11	86.66 ±3.13	0.152
	JLCA	8.79 ±4.44	8.73 ±4.49	0.831
	mFTA	14.62 ±6.98	14.71 ±6.96	0.544
Valgus knee deformity, mean degree ± SD	IMA	5.25 ±1.06	5.23 ±1.08	0.759
	LDFA	88.28 ±3.38	88.35 ±3.28	0.144
	MPTA	89.61 ±3.09	89.73 ±3.12	0.155
	JLCA valgus	7.26 ±3.88	7.31 ±3.84	0.867
	mFTA valgus	9.03 ±6.72	9.08 ±6.74	0.775

IMA=inter-mechanical-anatomical angle; LDFA=lateral distal femoral angle; MPTA=medial proximal tibia angle; JLCA=joint line convergence angle; mFTA=mechanical femorotibial angle

TABLE 2. Homogeneity of the two groups in gender and underlying diseases

		Groups		P	PJI		P
		Control group	Case group		No	Yes	
Gender	Female	531 (85.65%)	557 (85.43%)	0.913	1085 (85.5%)	3 (100%)	1.00
	Male	89 (14.35%)	95 (14.57%)		184 (14.5%)	0 (0%)	
Diabetes mellitus		124 (20%)	50 (7.67%)	<.001	173 (13.63%)	1 (33.33%)	0.357
Hypertension		247 (39.84%)	105 (16.1%)	<.001	350 (27.58%)	2 (66.67%)	0.187
Rheumatoid arthritis		11 (1.77%)	28 (4.29%)	0.009	38 (2.99%)	1 (33.33%)	0.089
Kidney disease		9 (1.45%)	4 (0.61%)	0.137	12 (0.95%)	1 (33.33%)	0.030
Heart valve replacement		1 (0.16%)	4 (0.61%)	0.198	5 (0.39%)	0 (0%)	1.00
Hypothyroidism		36 (5.81%)	25 (3.83%)	0.1	61 (4.81%)	0 (0%)	1.00
Dyslipidemia		64 (10.32%)	26 (3.99%)	<.001	90 (7.09%)	0 (0%)	1.00
Coronary artery bypass graft		28 (4.52%)	7 (1.07%)	<.001	35 (2.76%)	0 (0%)	1.00
Cerebral vascular accident		4 (0.65%)	4 (0.61%)	1	8 (0.63%)	0 (0%)	1.00
Asthma		13 (2.1%)	6 (0.92%)	0.084	19 (1.5%)	0 (0%)	1.00
Gout		4 (0.65%)	5 (0.77%)	1	9 (0.71%)	0 (0%)	1.00
Parkinson disease		1 (0.16%)	2 (0.31%)	1.000	3 (0.24%)	0 (0%)	1.00
Esophageal spasm		1 (0.16%)	0 (0%)	0.487	1 (0.08%)	0 (0%)	1.00
Peptic ulcer		1 (0.16%)	0 (0%)	0.487	1 (0.08%)	0 (0%)	1.00
Past medical history of breast cancer		1 (0.16%)	0 (0%)	0.487	1 (0.08%)	0 (0%)	1.00
Myelodysplasia		1 (0.16%)	1 (0.15%)	1.000	2 (0.16%)	0 (0%)	1.00
Psychotic disorder		0 (0%)	4 (0.61%)	0.125	4 (0.32%)	0 (0%)	1.00
Cerebral shunt		1 (0.16%)	0 (0%)	0.487	1 (0.08%)	0 (0%)	1.00
Sleep apnea		0 (0%)	1 (0.15%)	1.000	1 (0.08%)	0 (0%)	1.00
Psoriasis		0 (0%)	1 (0.15%)	1.000	0 (0%)	1 (33.33%)	.885

Patient number	Group	Age	Gender	DM	HTN	RA
1	Without vancomycin-ceftazidime injection	61	female	no	no	no
2	Without vancomycin-ceftazidime injection	72	female	yes	yes	no
3	With vancomycin-ceftazidime injection	57	female	no	yes	yes

TABLE 3. Description of PJI patients

control groups was not statistically significant (P=0.139).

Although the control and case groups were not homogeneous in terms of diabetes mellitus, hypertension, dyslipidemia and coronary artery bypass graft, the frequency of these conditions was higher in the control group. Also, the two groups were not homogeneous in terms of rheumatoid arthritis, but the frequency of this disease was higher in the case group. Both groups were homogeneous in terms of other diseases. According to Table 2, among underlying diseases, only kidney disease was considered a risk factor for PJI, while other diseases were not related to the increase in the incidence of PJI. As such, these factors were not regarded as confounding variables in the present study. The results of Fisher's exact test showed that gender did not have a statistically significant relationship with the incidence of infection and among underlying diseases, kidney disease had a statistically significant relationship with the incidence of infection; thus, we noticed that the chance of infection was 52 times higher in patients with kidney disease as an underlying disease than those without kidney disease (P=0.002) (Table 2).

An infection occurred in only two of the 620 patients in the control group and one of the 652 patients in the case group (Table 3). According to data summarized in Table 4, the administration of vancomycin/ceftazidime in the experimental group did not result in a significant reduction in the risk of PJI (P=0.615), as shown by the fact that only one patient in the case group was infected compared to the control group.

Patient number 2 was diagnosed with *E. coli*, whereas patients number 1 and 3 were diagnosed with *Staphylococcus epidermidis*. All three patients had PJI, but only patient number 3 was injected with intra-articular vancomycin/ceftazidime combination, while the remaing ones did not receive the study medication as they were included in the control group.

		Infection		Total	P-value
		no	yes		
Group	Control	618	2	620	0.615*
		48.7%	66.7%	48.7%	
	Case	651	1	652	
		51.3%	33.3%	51.3%	
Total		1269	3	1272	
		100.0%	100.0%	100.0%	

*Fisher's exact test

TABLE 4. Relationship between injecting or not injecting antibiotics with the incidence of infection among study patients

For patient number 2 in the control group, treatment consisted of taking out her polyethylene and changing it in addition to a washing out procedure along with debridement that was caused by infection, whereas for the other two infected patients, we took out the polyethylene, perfomed washing with alcohol and betadine, and then we placed it back.

The results of Fisher's exact test showed that there was no statistically significant relationship between injecting antibiotics and the incidence of infection among 95% of patients (P=.615) (Table 4). Multiple logistic regression with adjustment on the kidney disease variable showed that injecting antibiotics had no statistically significant relationship with the incidence of infection (P=0.689). ❑

DISCUSSION

Prosthetic joint infection is a notable surgical complication that results in heightened postoperative morbidity and mortality as well as a substantial increase in healthcare expenses due to the requirements of reoperation, extended hospital stays and prolonged antibiotic treatment. Various perioperative approaches are presently employed to mitigate the occurrence of infection. Antibiotics administered at the surgical site have been commonly used for the treatment and prophylaxis of infections and osteomyelitis, often blended with bone cement. The recent literature suggests that the direct ap-

plication of antibiotic powder onto the surgical wound bed prior to closure can be a viable, safe and cost-effective strategy for perioperative prophylaxis against infection, particularly in spinal surgeries. Specifically, vancomycin powder has been identified as an effective agent for this purpose. Pharmacokinetics have also explored the safety of administering vancomycin powder topically onto the operative wound bed. By employing this method, elevated therapeutic and concentration levels of antibiotics are achieved in the surgical wound, leading to an excellent minimum inhibitory concentration (MIC) and reduced levels of toxicity and serum concentration.

Out of a total of 1270 TKAs conducted during the duration of the present study, only 1270 patients who had a documented follow-up period of at least two years were included. The demographic and radiographic features of both groups were comparable. Many studies about TKA have shown that there was a significant difference between the groups of patients with and without intraarticular antibiotic injection, while others reported contrasting results. Several researchers have examined the efficacy of intra-wound vancomycin powder (VP) in the prevention of infection following TJA. Tahmasebi *et al* found that local application of vancomycin during TKA surgery could be a justifiable approach for prophylaxis against infection, resulting in a statistically significant decrease in the risk of PJI (11). But we did not see such an association, which might be explained by the fact that Tahmasebi *et al* used sole vancomycin and it was performed 10 years before our study, when antimicrobial resistance was probably less than our study time. According to Dial *et al*, patients who received one gram of VP prior to wound closure, following total hip arthroplasty, exhibited a notably lower incidence of PJI (7). Through a synthesis of evidence *via* meta-analysis, Peng *et al* found that the use of local VP application during primary TJA could effectively reduce the incidence of PJI without altering the bacterial spectrum involved (12). In contrast to the untreated group, Patel *et al* observed a reduced overall infection rate and incidence of PJI in the cohort treated with vancomycin (13). The divergent outcomes between our study and previous reports may be attributed to various factors. One of them is represented by differences in study design, including the patient population, surgical technique and definition of prosthetic joint infection. Variations in the administration of vancomycin powder, such as differences in dosage, timing and application method, represent another possible explanation for the divergent outcomes observed by us. Additionally, variations in the length of follow-up and criteria used to assess infection could also contribute to the heterogeneous results. It is important to consider the overall body of evidence and the limitations of individual studies when evaluating the effectiveness of a particular intervention.

In line with our findings, Hanada *et al* found no significant efficacy of vancomycin on the PJI rates (14). Ibrahim *et al* documented that the use of intra-wound VP had no discernible effect on infection rates in primary TKA (15). In contrast, Jian Wei *et al* conducted an investigation into the appropriate dosage, efficacy and safety of intra-articular VP for prophylaxis against infection following TKA, employing a rat model that did not reveal any significant technical outcomes after the utilization of intra-articular antibiotic injections (16). A possible hypothesis could have arisen from this review of the literature that newer studies in recent years showed less efficacy of intra-articular injection of antibiotics in reducing the rate of PJI.

Study limitations

Given the retrospective nature of the present study, there is a possibility of selection bias being introduced. The inclusion of historical control subjects and the absence of randomization increases the likelihood of selection bias. However, further investigation is required to precisely determine the impact of intra-wound vancomycin and ceftazidime on the incidence of deep infection following TKA. To this end, prospective randomized controlled trials specifically designed for the use of these agents in knee arthroplasty surgery are necessary. Another limitation of our study was not accounting for aseptic complications. ❑

CONCLUSION

This was the first retrospective historical cohort study in which all arthroplasties were performed by the same surgical team in the same hospital by using prosthetics of the same type. We found no superiority of intra-articular antibiotic injection. To ensure a more reliable and well-founded recommendation for the utiliza-

tion of topical vancomycin and ceftazidime as prophylaxis against PJI, additional prospective and randomized studies are needed. Such studies should aim to control for risk factors and homogenize the study sample, standardize the dosage and technique for topical antibiotic administration, determine the minimum effective local concentration, evaluate the potential risks of developing resistant bacterial flora or alterations in the microbiological profile of PJI, and identify patient profiles that are most suitable for topical prophylaxis (such as patients with risk factors and medical centers with high PJI rates). In future studies, the implementation of blinded trials would be of significant benefit, as they would help to eliminate biases such as surgeon's preferences and idiosyncrasies of the surgical techniques employed. ❑

Conflicts of interest: none declared.
Financial support: none declared.

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