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Original Research Article

Efficacy and safety of locally-applied vancomycin powder injection for the prevention of prosthetic joint infection

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Abstract

Purpose: *To determine the efficacy and safety of locally-applied vancomycin powder injection as precaution against prosthetic joint infection (PJI).*
Methods: *A total of ninety subjects on admission in Department of Limb and Joint Surgery, PLA Medical Center, who underwent surgery for arthroplasty of knee and hip, were selected for this study. They were divided into two groups comprising control group (n = 45) given routine preventive antibiotic therapy as well as treatment group (n = 45) which received routine prophylactic antibiotics in combination with vancomycin therapy. PJI and the incidence of adverse reactions within 3 months after surgery were recorded. Body temperature of the patients was recorded with a thermometer. The number of neutrophils was measured by flow cytometry, while the expression levels of IL-6 and hs-CRP in peripheral blood were determined using enzyme-linked immunosorbent assay (ELISA) preoperatively and at 24, 72 and 168 h post- therapy.*
Results: *At 90 days post-therapy, there was obviously significant reduction in the degree of PJI in the vancomycin-treated subjects compared with control group ($p > 0.05$). Moreover, within 3 days, normothermia, lowered neutrophil population and downregulated expressions of Il-6 and hs-CRP were seen in the vancomycin group, when compared to control subjects ($p < 0.05$). However, there was no significant difference in the incidence of adverse reactions between the treatment and control groups after therapy ($p > 0.05$).*
Conclusion: *Topical application of vancomycin powder injection is safe, and regulates the body temperature of PJI patients in the short-term after surgery. Moreover, it decreases the levels of inflammatory indices. However, further clinical trials should be carried out prior to application in clinical practice.*

Keywords: *Vancomycin, Prosthetic joint infection, Neutrophil count, IL-6, High-sensitivity C-reactive protein*

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INTRODUCTION

The number of patients who receive joint replacements worldwide is increasing year by year. According to statistics, in 2021, more than 341,000 patients in the United States received hip arthroplasty, while 719,000 patients received knee arthroplasty [1]. The main reason for readmission of patients undergoing joint replacement is artificial joint infection (PJI), and

the annual incidence of readmission is approximately five percent [2]. The annual cost of re-hospitalization to PJI patients in the United States is about 566 million dollars, and it may reach 1.6 billion dollars or more by 2022 [3].

The microorganism responsible for PJI is *S. aureus.* A species of *Staphylococcus* which is insensitive to methicillin (MRSA), has the potential to induce infection and limit the effect of antibiotics. At this time, local application of antibiotics greatly increases the local concentration of antibiotic at the wound, and at the same time, minimizes blood drug level, thereby reducing unwanted side effects. A recent study on potential of local application of vancomycin powder to reduce the possibility of infection after spinal surgery has been evaluated [4,5]. However, from the current results, vancomycin rarely prevents PJI through local treatment. In this study, corresponding evidence is provided for the treatment of PJI patients with vancomycin, as well as reductions in infection rate and incidence of related adverse reactions, through analysis and comparison with conventional regimen.

METHODS

Baseline clinical data

A total number of ninety in-patients with full arthroplasty of hip as well as knee arthroplasty in the Department of Limb and Joint Surgery, PLA Medical Center from Jan 2018 to Dec 2019 served as subjects in this research. The study was ratified by the ethics committee of Army Medical Center of PLA (approval no. 2018-0876), and carried out in line with the guidelines of the Declaration of Helsinki [6].

The patients were randomly assigned to vancomycin group which was treatment group (n = 45), and conventional regimen group, which was control group (n = 45). There were 24 male patients and 21 female patients in the treatment group, and their average age was 67.89 ± 5.48 years. In this group, 30 patients had THA, while 15 had TKA. A total of 29 patients underwent unilateral artificial joint replacement, while 16 patients underwent bilateral artificial joint replacement. The control group comprised 23 males and 22 females, and their average age was 68.02 ± 5.35 years. The THA was performed in 29 patients, while TKA was performed in 16 patients. In this group, 30 patients underwent unilateral joint replacement, while 15 patients underwent bilateral joint replacement. There were no obvious differences in baseline clinical data between the two groups.

Conditions for inclusion

Patients in the following categories were included in the study: patients within the age range of 60 - 80 years; patients for unilateral arthroplasty of hip as well as knee arthroplasty; those who tolerated the drugs applied in this research; patients who cooperated during the study and strictly followed the prescribed treatment plan, and patients who submitted signed statement of willingness to participate.

Conditions for exclusion

The following categories of patients were excluded from the study: subjects who had bone breakages due to other pathologies outside osteoporosis; patients with fractures in other parts (e.g., femoral shaft fracture); patients suffering from serious medical conditions who could not be operated on after medical counselling and therapy; those who were heavy drinkers or who took other drugs like glucocorticoids likely to affect the research outcomes; subjects such as those with mental diseases who could not comply with the therapy.

Treatments

All experimental subjects were treated with conventional preventive antibiotics: 1 g of cefazolin was given to the patients within 30 minutes before surgery, followed by 1 g administered post-surgery at 8-hour intervals. For subjects with adverse reaction to cefazolin, the researchers gave 0.6g clindamycin 30 minutes before the operation, and an additional 0.6g every 8 hours after the operation. The duration of antibiotic treatment in both groups was 48 hours. In the treatment group, local injection of vancomycin was done, in addition to conventional antibiotic treatment. Vancomycin (0.5g) was injected into the acetabular fossa at the surgical incision. Following the femoral head mold test, the joint was dislocated, and another dose of vancomycin (0.5g) was injected into the medullary cavity. For patients with unilateral joint replacement, 1 g vancomycin powder was injected at incision site. At the same time, one gram of vancomycin powder was injected on both sides of the surgical wound of patients undergoing bilateral joint replacement.

Evaluation of indices/parameters

Patient's body temperature

The body temperature of each patient was recorded with a thermometer before surgery, and 1, 3, and 7 days after treatment.

Number of neutrophils

Peripheral blood (5 mL) was taken each patient in both groups, and after heparin anticoagulation, neutrophils were isolated, and 6% Dextran-40 solution erythrocytes was used to extract and separate neutrophils. Flow cytometry was applied to determine the number of neutrophils.

Expression levels of interleukin-6 (IL-6) and high-sensitivity C-reactive protein (hs-CRP)

Venous blood (10 mL) was drawn from each patient on an empty stomach early in the morning. After standing at 4°C for 30min, centrifugation was performed at 3000 rpm for 10 minutes. The serum was aspirated and put in EP tubes and kept preserved at - 80 °C. The expression levels of serum IL-6 and hs-CRP in patients were assayed using ELISA kit.

Criteria for diagnosis of PJI

These stem from diagnostic criteria of Alexander: (1) presence of fistulas in impacted knee or hip in the course of therapy implied PJI. (2) Diaresis was diagnosed if two or more of the following conditions existed: (a) presence of bacteria in sample of fluid from the joint, or if the laboratory department of our hospital detected problematic hip or knee joints or other intraoperative tissue samples; (b) if marked elevation in neutrophil population count was found in tissue samples during surgery; (c) PJI verified using clinical manifestations (for example: general pyrexia, joint ache and more); laboratory investigations as well as radiography.

Statistics

All data were analyzed using the statistical analysis tool, SPSS 23.0 software. Numerical data are expressed as percentage (%), and were compared using χ^2 test. Quantitative data are shown as mean ± standard deviation (SD), and were compared with independent samples *t*-test. Values of $p < 0.05$ were regarded as statistically significant.

RESULTS

Incidence of PJI

As indicated in Table 1, 90 days after therapy, the incidence of PJI in the treatment group was markedly lower than that of the control group ($p < 0.05$). Six patients had PJI, among which there were 4 cases of superficial incision infection and 2 cases of deep tissue infection. *Staphylococcus aureus* was detected in 3 cases, while *Escherichia coli* was detected in 2 cases. The case of one patient was of negative etiology.

Table 1: Analysis of PJI cases in the 2 groups

Group	Without infection	With infection	Infection rate (%)
Control group (n=45)	39	6	13.33
Treatment group (n=45)	45	0	0.00
χ^2			4.360
P-value			0.037

Body temperature

In the short-term (1 to 3 days) after therapy, the mean body temperature of patients in the therapy group was below that in the control group ($p < 0.05$). At preoperative stage, and at 7 days post-therapy, there was no statistically significant variation in body temperature between the two groups ($p > 0.05$; Table 2).

Body neutrophil count

In the short-term period (1 to 3 days after therapy), compared with control group, the neutrophil count was lower in treatment group ($p < 0.05$). However, there were no obvious statistically significant differences between the neutrophil counts of both groups at preoperative and one week after therapy ($p > 0.05$; Table 3).

Table 2: Changes in body temperature (mean ± SD, n = 45)

	Body temperature (°C)			
Group	**Preoperative**	***Postoperative 1st day***	***Postoperative 3rd day***	***Postoperative 7th day***
Treatment	36.5±0.39	37.4±0.32	37.2±0.39	36.6±0.41
Control	36.6±0.40	37.7±0.33	37.5±0.40	36.7±0.40
T	1.201	4.378	3.602	1.171
P	0.233	0.000	0.001	0.245

Table 3: Serum neutrophil count (mean ± SD, n = 45)

	Neutrophil count (×10^9/L)			
Group	***Preoperative***	***Postoperative 1st day***	***Postoperative 3rd day***	***Postoperative 7th day***
Treatment	5.4±0.50	6.8±0.61	6.4±0.51	6.2±0.50
Control	5.5±0.51	7.5±0.62	6.8±0.54	6.3±0.49
T	0.939	5.399	3.613	0.958
P-value	0.350	0.000	0.000	0.341

Table 4: Serum IL-6 levels (mean ± SD, n = 45)

	IL-6 (pg/mL)			
Group	**Preoperative**	**Postoperative 1st day**	**Postoperative 3rd day**	**Postoperative 7th day**
Treatment	31.2±5.45	84.7±6.24	62.5±5.48	46.4±3.29
Control	31.5±5.39	92.3±6.35	68.6±5.56	46.7±3.42
T	0.263	5.727	5.242	0.424
P	0.794	0.000	0.000	0.673

Table 5: Changes in serum CRP levels (mean ± SD, n = 45)

	CRP (mg/L))			
Group	**Preoperative**	**Postoperative 1st day**	**Postoperative 3rd day**	**Postoperative 7th day**
Treatment	9.0±1.2	37.8±3.43	28.3±3.28	19.0±2.14
Control	8.9±1.1	47.8±4.35	36.4±3.19	19.2±2.11
T	0.412	12.109	11.876	0.446
P-value	0.681	0.000	0.000	0.656

Serum IL-6 levels

In the short-term period (1 to 3 days after therapy, the IL-6 levels were lower in treatment group than in the control group ($p < 0.05$). The levels of IL-6 in the body at preoperative period and at one week after therapy were not statistically different between the two groups ($p > 0.05$; Table 4).

Serum CRP levels

In a short-term period (1 and 3 days after therapy), serum CRP was lower in the vancomycin group, when compared with control group. However, CRP levels at preoperative period and at 7th day post-surgery were not significantly different in the 2 groups ($p > 0.05$; Table 5).

Incidence of post-surgery unwanted reactions

Three unwanted reactions were seen in the treatment group, while the control group had two cases. There were was no statistically obvious difference in unwanted side effects between the two groups ($\chi 2 = 0.000$, $p = 1.000$).To be specific, therapy group had 1 case each of rash, hemocytopenia as well as kidney malfunction, while rashes occurred in two control subjects. However, clinical treatment helped the affected patients to get better.

DISCUSSION

In recent years, with the advancements in manufacturing technique used for artificial joint prosthesis, as well as upgrade and growth of surgery and anesthesiology during the therapy, artificial joint replacement has become more and more popular. However, postoperative PJI has always been a burden to patients. As far back as the 1980s, the incidence of PJI was up to 9.1 percent [7]. However, through these advances in surgery and anesthesiology, the prevalence of PJI is currently between 0.2 and 4 percent [8]. If not treated properly, PJI is a source of anxiety and financial burden to the subjects and family members, and it may be fatal [3]. The major microorganism that causes PJI is *S. aureus* [9].

However, PJI due to microbes such as *Fusobacterium nucleatum* [10] and non-*Candida albicans* [11] have been recently reported to also occur. Due to the widespread use of antibiotics, there are more and more PJI caused by drug-resistant strains. Several susceptible bacteria may even become multi-drug resistant, thereby reducing the availability of effective antibiotics [12]. The pathogens lead to infection around the prosthesis majorly due to direct pollution and

blood-borne infection [13]. Direct pollution is majorly caused by inadequate disinfection of surgical instruments, implanted prosthesis as well as surgical sites. Recently, China and other countries have conducted studies on the risk factors for prosthesis. For example, AAOS directives [8] indicates that the relevant risk elements for PJI post-arthroplasty risk are skin infection, overweight as well as operation time longer than 2.5 hours. There are other risk factors for PJI, e.g. history of bacteremia and fungemia within one year, as well as history of skin diseases, in addition to MRSA history and acute infection history in other parts within 3 years. Besides, other hazard elements are post-surgery fibrillation of arteries, and myocardial infarction [14]. In recent years, western countries reported PJI cases resulting from consumption of Asian blackfish and snakehead fish. This suggests that "sashimi dish" should be regarded as one of the causative factors for PJI.

Prevention of perioperative infection may reduce the probability of second operation in patients, and also decrease the associated medical costs. After surgery, ischemia or hematoma that happen usually in the wound decreases the absorption capacity of antibiotics [15]. Curremtly, orthopedic doctors prefer to use antibiotics (with high drug concentration and low systemic toxicity) which are applied locally for infection prevention. Local administration of vancomycin powder for prevention of postoperative infection is very effective in spinal surgery in adults or children. In a retrospective study of 1732 patients undergoing thoracolumbar fusion, Sweet *et al.* found that local application of vancomycin powder reduced the incidence of infection from 2.6 to 0.2% [16]. In the study group, 2g vancomycin was used: 1g in the bone graft, while 1 g was applied in deep tissue and incision site in the period of closure of the surgical incision. After the following 2.5 years, no patient had any adverse flection which was relevant to local application of vancomycin powder.

Qadir *et al* demonstrated that local application of vancomycin powder significantly decreased the spinal trauma infection rate of patients by 13 % to 0 following posterior spinal fusion operation (PSFO) [17]. In addition, the report showed local application of vancomycin reduced the infection incidence in patients undergoing PSFO from 10.9 to 2.5 % [18]. However, currently, there are limited research on patients undergoing artificial joint replacement. With the application of bioprosthesis, the usage of antimicrobial-impregnated bone cements has decreased. In this study, it is concluded that local application of vancomycin powder reduced PJI occurrence following arthroplasty. However, there is still need to determine whether the locally applied vancomycin may cause allergic reflection, acute renal failure, as well as any other untoward reactions.

In the past, Gans *et al* studied the renal function of 1828 hip and knee replacement patients, and the outcome revealed a sharp increase in the risk of acute renal failure when cefazolin and vancomycin were locally applied in combination as opposed to when cefazolin was used alone [19]. In the report, unwanted side reactions were comparable in the groups. However, there were no verifications confirming the accuracy of its half-life and precipitation potential in joint fluid. In addition, it is very important to analyze the effect of local vancomycin application on wear at prosthesis joint. Therefore, these issues require high-quality study. Now, PJI is diagnosed using clinical symptoms and pathogen culture of tissues around the prosthesis [14]. Treatment is still necessary, but clinical prevention is increasingly crucial. Therefore, physicians may guide clinicians in postoperative preventive medication, while the physical condition of the patients can be fully studied by monitoring body temperature, hemogram as well as hs-CRP. The presence of infection can be detected in advance by monitoring the postoperative temperature. The temperature will probably rise within 72 h after the operation, and then it will be determined as an index of infection [20]. Neutrophil count is a common index for verifying the existence of infectious diseases. Under normal conditions, this index is measured via post-surgery blood test. In the body, hs-CRP has the function of immune regulation, that is, when there is obvious inflammatory reaction, its content will be significantly increased. In this research, locally applied vancomycin powder controlled pyrexia, reduced neutrophil population, and downregulated expressions of hs-CRP IL-6 and hs-CRP levels at 1 and 7 days post-surgery. These findings show that locally-applied vancomycin prevented the entry of inflammatory factors and thus reduced the possibility of infection.

CONCLUSION

Locally-applied vancomycin minimizes the occurrence of PJI in patients undergoing arthroplasty. It is relatively safe. However, there are currently only few related studies on its efficacy and toxicity. These need to be confirmed via high-quality investigations. Further research are needed to determine the effect of locally-applied vancomycin on wear at joints, and its

potential to increase presence of antibacterial-insensitive microbes.

DECLARATIONS

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Ethical approval

The study was ratified by the Ethics Committee of Army Medical Center of PLA (approval no. 2018-0876.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was completed by the authors listed in this article, and all liabilities pertaining to claims relating to the article detail will be undertaken by the authors. The study was originated and designed by Yu Wang and Keyun Peng. Yu Wang, Chengling Li and Keyun Peng collected, analyzed and explained the experimental data. Yu Wang and Chengling Li reformulated the manuscript for significant intellectual contents. All authors read and approved the final manuscript for publication.

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