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Vascular Graft Infection by *Staphylococcus aureus*: Efficacy of Cefazolin, Teicoplanin and Vancomycin Prophylaxis Protocols in a Rat Model

E. Atahan,[1*] M. Gul,[2] Y. Ergun[3] and E. Eroglu[1]

Departments of [1]Cardiovascular Surgery, [2]Microbiology, and [3]Pharmacology, School of Medicine, Kahramanmaras Sutcu Imam University, 46100, Turkey

Objectives. *Prophylactic efficiencies of cefazolin, teicoplanin and vancomycin in a dacron graft infection model caused by methicillin-susceptible (MSSA) or -resistant* Staphylococcus aureus *(MRSA) were investigated.*
Design. *Prospective, randomized, controlled animal study.*
Materials and methods. *Infections were established subcutaneously in the back of rats by implantation of Dacron prostheses followed by topical inoculation onto grafts of MSSA or MRSA. Experimental groups were as follows: Uncontaminated group (control), MSSA- or MRSA-contaminated and untreated groups, MSSA- or MRSA-contaminated groups treated with cefazolin, teicoplanin or vancomycin by one of three regimens (one day, two days, or three days regimen). Grafts were removed 7 days after the implantation and evaluated by using sonication and quantitative blood agar culture.*
Results. *Contaminated groups demonstrated graft infections. Cefazolin, teicoplanin and vancomycin profoundly prevented the graft infections in MSSA- or MRSA-contaminated groups. For each antibiotic regimen, the most effective prevention was achieved by the drugs given as three days regimen. For MSSA and MRSA, the order of the effectiveness was as follows: teicoplanin > vancomycin > cefazolin.*
Conclusion. *As a prophylactic agent, teicoplanin seems to be more effective than vancomycin and cefazolin against vascular graft infections caused by MSSA and MRSA in rats.*

Keywords: Vascular graft infection; Cefazolin; Glycopeptides; Teicoplanin; Vancomycin; Antibiotic prophylaxis.

Introduction

In vascular surgery, infections of prosthetic vascular grafts are one of the most serious and life-threatening complications and range from 2 to 6% of clean cases performed despite systemic prophylactic antibiotics and successful revascularization.[1,2] The mortality and amputation rates of prosthetic vascular graft infections are up to 20 and 57%, respectively.[3–6]

The causative organisms are mainly *S. auerus* and *S. epidermidis.*[1,7] In cardiac, thoracic, vascular and orthopaedic surgery, *Staphylococcus aureus* and coagulase-negative staphylococci (particularly *Staphylococcus epidermidis*) are responsible for 70 to 90% of postoperative infections. Other microorganisms, including diphteroids, aerobic and anaerobic streptococci and enteric gram-negative bacilli are involved to a much lesser extent.[8–10]

The most important strategies for the prevention of prosthetic infections are asepsis and perioperative administration of systemic antibiotics.[11–13] Cefazolin is still regarded as the first choice for prophylaxis in clean vascular surgery.[14] Teicoplanin is a glycopeptide antibiotic and has an excellent bactericidal activity against penicillinase-producing and methicillin-resistant *S. epidermidis and S.aureus*.[15,16] Teicoplanin has an antibacterial spectrum similar to that of vancomycin but longer half-life and less serious side effects.[17–21] Unlike vancomycin, teicoplanin is well tolerated after intramuscular administration, and its prolonged half-life is suitable for once-daily dosing.[22] Vancomycin is used as a parenteral antibiotic therapy to treat infections caused by staphylococcal infections since the emergence of methicillin-resistant staphylococci.[23,24]

Despite systemic prophylaxis, prosthetic vascular graft infection still takes place. In cardiac surgery, it was reported that single-dose antimicrobial prophylaxis

*Corresponding author. Dr. E. Atahan, MD, Department of Cardiovascular Surgery, School of Medicine, Kahramanmaras Sutcu Imam University, 46100, Turkiye.
E-mail address: atahanerhan@hotmail.com

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was as effective as a two days regimen[25] The aim of the present study was to compare the in vivo efficacies of a single-dose to those of a multiple-dose antibiotic prophylaxis for cefazolin, teicoplanin and vancomycin. For this purpose each antibiotic was administered by one of three regimens (one day, two days, or three days regimen). Additionally, we evaluated the bacterial adherence to a dacron prosthetic graft by MSSA and MRSA and the effect of antibiotic prophylaxis duration on the prevention of MSSA and MRSA graft infection.

Materials and Methods

Organisms

The commercially available methicillin-susceptible quality control strain of *S.aureus* ATCC 29213 and methicillin-resistant *S.aureus* ATCC 25923 used in this study were isolated from a clinical specimen submitted for routine bacteriological investigation to the Department of Microbiology, Faculty of Medicine, Kahramanmaras Sutcu Imam University, Turkey.

Drugs

Cefazolin (Cefamezin, Eczacibasi, Istanbul), Vancomycin (Vancomycin Hydrochloride, DBL, Mayne Pharma Plc, UK) and Teicoplanin (Targocid, Aventis, Turkey) were diluted in accordance with manufacturers' recommendations, yielding 1 mg/ml stock solutions. Solutions of drug were fresh on the day of assay.

Susceptibility testing

The antimicrobial susceptibilities of MSSA and MRSA strains were determined by using the micro-broth dilution method, according to the procedures outlined by the National Committee for Clinical Laboratory Standards.[26]

Rat model

This study was approved by the Ethics Committee of School of Medicine, Kahramanmaras Sutcu Imam University, Turkey. One hundred and fifty four adult female Sprague−Dawley rats (weight range, 200−250 g) were studied. All rats had free access to standard rat chow and tap water. Each group was comprised of 7 animals. The study included a group with no graft contamination and no antibiotic prophylaxis (control group); MSSA- or MRSA-contaminated groups that did not receive any antibiotic prophylaxis (Contaminated and untreated groups; MS1, MR1); two contaminated groups that received perioperative cefazolin (a single dose, 30 mg/kg, IP) half an hour before implantation as one day regimen (MS2, MR2); two contaminated groups that received perioperative cefazolin (30 mg/kg, IP each) half an hour before and 24 h after implantation as two days regimen (MS3, MR3); two contaminated groups that received perioperative cefazolin (30 mg/kg, IP each) half an hour before, 24 h and 48 h after implantation as three days regimen (MS4, MR4); two contaminated groups that received perioperative teicoplanin (a single dose, 10 mg/kg, IP) half an hour before implantation as one day regimen (MS5, MR5); two contaminated groups that received perioperative teicoplanin (10 mg/kg, IP each) half an hour before and 24 h after implantation as two days regimen (MS6, MR6); two contaminated groups that received perioperative teicoplanin (10 mg/kg, IP each) half an hour before, 24 h and 48 h after implantation as three days regimen (MS7, MR7); two contaminated groups that received perioperative vancomycin (a single dose, 10 mg/kg, IP) half an hour before implantation as one day regimen (MS8, MR8); two contaminated groups that received perioperative vancomycin (10 mg/kg, IP each) half an hour before and 24 h after implantation as two days regimen (MS9, MR9); two contaminated groups that received perioperative teicoplanin (10 mg/kg, IP each) half an hour before, 24 h and 48 h after implantation as three days regimen (MS10, MR10).

Under intraperitoneal ketamine hydrochloride (30 mg/kg, Ketalar, Pfizer, Turkey) and xylazine hydrochloride (10 mg/kg, Rompun, Bayer, Turkey) anesthesia the backs of animals were shaved and the skin cleaned with 10% povidone iodine solution. One subcutaneous pocket was made on the right side of the median line by a 1.5 cm incision. Aseptically, 1 cm^2 sterile gelatin-sealed Dacron grafts (Gelseal; Sulzer Vascutek Ltd, UK) were implanted into the pockets. The pockets were closed by 5/0 polypropylene sutures (Dogsan Ltd, Turkey), and saline solution (1 mL) containing the MSSA or MRSA strain at a concentration of 2×10^7 CFU/mL was inoculated on the graft using a tuberculin syringe to create a subcutaneous fluid-filled pocket. The animals were returned to individual cages and thoroughly examined daily. All grafts were explanted after 7 days following implantation.

Assessment of the infection

The explanted grafts were washed in sterile saline solution, placed in tubes containing 10 mL of

phosphate-buffered saline solution and sonicated for 5 min to remove the adherent bacteria from the grafts. Quantification of viable bacteria was performed by preparing serial 10 fold dilutions (0.1 ml) of the bacterial suspensions in 10 mM buffer and by culturing each dilution on blood agar plates. All plates were incubated at 37° C for 48 h and evaluated for the presence of MSSA and MRSA. The organisms were quantified by counting the number of colony forming units (CFU) per plate. The limit of detection for this method was approximately 50 CFU/cm^2 of graft tissue.

Statistical analysis

Quantitative culture results were presented as arithmetic mean ± standard deviation (S.D.). Comparisons of the results were performed by Kruskal-Wallis test, and multiple comparisons between the groups were performed with Mann-Whitney-U test. Differences were considered statistically significant when $P < 0.05$.

Results

None of the animals included in any group died or had clinical evidence of drug or sepsis related adverse effects, such as local signs of perigraft inflammation, anorexia, vomiting, diarrhoea, and behavioural alterations. However, polydipsia was seen in the vancomycin-treated groups.

None of the animals included in the control group had either anatomic or microbiological evidence of graft infection. In contrast, all rats in the contaminated and untreated groups that did not receive any antibiotic prophylaxis (MS1, MR1) demonstrated graft infections, evidenced by the quantitative culture results showing $4.4 \times 10^7 \pm 1.3 \times 10^6$ and $5.5 \times 10^7 \pm 4.8 \times 10^6$ CFU/cm^2 (Tables 1 and 2). Cefazolin profoundly prevented the graft infection by each protocol assessed (MS2-4, MR2-4), and the most effective prevention was observed in MS4 and MR4 (Tables 1 and 2) (Kruskall-Wallis test, $P < 0.001$). The results from teicoplanin-treated groups (MS5-7 and MR5-7) showed lower bacterial numbers as assessed by quantitative graft cultures when compared to that of MS1 or MR1 (Tables 1 and 2) (Kruskall-Wallis test, $P < 0.001$). Three days regimen of this drug abolished bacterial counts of each strain. Similarly, vancomycin-treated groups (MS8-10, MR8-10) exerted attenuation in bacterial counts (Tables 1 and 2) (Kruskall-Wallis test, $P < 0.001$). The most effective groups of vancomycin treatment were MS10 and MR10 (Tables 1 and 2).

Table 1. Quantitative microbiological results of the *in vivo* experiments

Groups[a]	Intraperitoneal perioperative drug[b]	Quantitative graft culture (CFU/cm^2)	*P* values (Mann-Whitney U test)
Control	-	0	
MS1	-	$4.4 \times 10^7 \pm 1.3 \times 10^6$	
MS2[c]	Cefazolin (1 day)	$1.2 \times 10^3 \pm 1.3 \times 10^2$	0.002
MS3[c]	Cefazolin (2 days)	$4.8 \times 10^2 \pm 5.4 \times 10^1$	0.002
MS4[c]	Cefazolin (3 days)	$1.2 \times 10^2 \pm 1.7 \times 10^1$	0.002
MS5[c]	Teicoplanin (1 day)	$2.6 \times 10^2 \pm 1.4 \times 10^1$	0.002
MS6[c]	Teicoplanin (2 days)	$1.3 \times 10^1 \pm 0.1 \times 10^1$	0.002
MS7[c]	Teicoplanin (3 days)	0	0.001
MS8[c]	Vancomycin (1 day)	$3.5 \times 10^2 \pm 0.2 \times 10^1$	0.002
MS9[c]	Vancomycin (2 days)	$1.2 \times 10^2 \pm 0.1 \times 10^1$	0.002
MS10[c]	Vancomycin (3 days)	$1.0 \times 10^1 \pm 1.0 \times 10^1$	0.002

[a] Each group was comprised of 7 animals; MS1-MS10, groups of animals infected with methicillin-susceptible *S.aureus* ATCC 29213.
[b] Cefazolin, Teicoplanin and Vancomycin; 30 mg/kg, 10 mg/kg, 10 mg/kg, respectively.
[c] Statistically significant when a comparison was made versus MS1.

For MSSA and MRSA, the most effective antibiotic seemed to be teicoplanin when compared to vancomycin and cefazolin since it has completely negated the bacterial count in the 3 days regimen.

Discussion

In the present study, cefazolin (30 mg/kg) administered as one day, two- and three-days regimens significantly decreased the bacterial count of either MSSA

Table 2. Quantitative microbiological results of the *in vivo* experiments

Groups[a]	Intraperitoneal perioperative drug[b]	Quantitative graft culture (CFU/cm^2)	*P* values (Mann-Whitney U test)
Control	-	0	
MR1	-	$5.5 \times 10^7 \pm 4.8 \times 10^6$	
MR2[c]	Cefazolin (1 day)	$3.2 \times 10^5 \pm 2.6 \times 10^4$	0.002
MR3[c]	Cefazolin (2 days)	$5.5 \times 10^4 \pm 4.3 \times 10^3$	0.002
MR4[c]	Cefazolin (3 days)	$2.6 \times 10^3 \pm 1.8 \times 10^3$	0.002
MR5[c]	Teicoplanin (1 day)	$4.1 \times 10^3 \pm 1.7 \times 10^2$	0.002
MR6[c]	Teicoplanin (2 days)	$2.1 \times 10^2 \pm 1.5 \times 10^2$	0.002
MR7[c]	Teicoplanin (3 days)	0	0.001
MR8[c]	Vancomycin (1 day)	$7.1 \times 10^3 \pm 1.8 \times 10^2$	0.002
MR9[c]	Vancomycin (2 days)	$4.2 \times 10^3 \pm 2.3 \times 10^2$	0.002
MR10[c]	Vancomycin (3 days)	$1.3 \times 10^2 \pm 1.2 \times 10^2$	0.002

[a] Each group was comprised of 7 animals; MR1-MR10, groups of animals infected with methicillin-resistant *S.aureus* ATCC 25923.
[b] Cefazolin, Teicoplanin and Vancomycin; 30 mg/kg, 10 mg/kg, 10 mg/kg, respectively.
[c] Statistically significant when a comparison was made versus MR1.

or MRSA compared to control. Among these regimens the most effective one was the latter protocol. In a previous study, the effect of cefazolin in comparison with placebo was evaluated during 565 arterial reconstructive operations and a highly significant difference in the infection rates was found: 6.8% for placebo recipients versus 0.9% for cefazolin recipients among.[27] Shue *et al.* reported that the most common form of antibiotic prophylaxis used in vascular surgery is a systemic, broad spectrum first generation cephalosporin (especially cefazolin).[28] However, prophylaxis alone cannot prevent prosthetic vascular graft infection. Alternative concepts to reduce this risk are of major clinical interest. Although cephalosporins and in particular cefazolin are of great importance in preventing vascular graft infections, resistance to these drugs began to emerge. Hence, the glycopeptides such as teicoplanin and vancomycin potentially effective against MRSA have appeared as an alternative and effective treatment for staphylococcal infections.

To test whether or not teicoplanin is a useful option as a prophylactic agent, we used teicoplanin in our rat model in a similar fashion to that of cefazolin. In all the regimens tested, teicoplanin was found to be effective against MSSA or MRSA since bacterial counts were significantly lower than those obtained in the control group. Again the most effective treatment was detected to be the three-dose regimen, and teicoplanin was also shown to be more effective than cefazoline. When considering the great difference in the efficacy of these drugs, teicoplanin seems to be a more rationale option than cefazolin in preventing vascular graft infections. Similarly, Zanetti *et al.* compared vancomycin and cefazolin as antibiotic prophylaxis in coronary artery surgery and they concluded that perioperative antibiotic prophylaxis with vancomycin is usually more effective and less expensive than cefazolin.[29] On the other hand, Marroni *et al.* compared teicoplanin and cefazolin as antibiotic prophylaxis in prosthetic vascular surgery. They found that surgical-site infections occurred in 5.9% of teicoplanin recipients (4.2% wound infection, 1.7% graft infection) and 1.7% of cefazolin recipients (1.7% wound infection, 0% graft infection). They concluded that cefazolin could still be regarded as the drug of choice for prophylaxis in clean vascular surgery.[30] Likewise, Saginur *et al.* performed a multi-center double-blind randomized controlled trial comparing teicoplanin, a glycopeptide antibiotic, with cefazolin. A total of 3027 adult patients undergoing elective coronary artery and valve operations, or both were randomized to a single dose of teicoplanin (15 mg/kg) or a 2-day course of cefazolin (2 g initial dose, followed by 1 g every 8 hours for 6 more doses). They reported that cefazolin was more effective prophylaxis than teicoplanin against postoperative wound infections after elective cardiac operations.[31]

In another study of elective vascular surgery, the efficacy of single dose of teicoplanin (6 mg/kg) was compared with multiple doses of cefradine plus metronidazole (three doses each). No significant differences in wound infection rates were found between the two groups.[32] In accordance, Vardakas *et al.* presented a meta-analysis of randomized controlled trials evaluated the effectiveness and safety of teicoplanin compared to first- or second-generation cefalosporins for perioperative prophylaxis in orthopaedic and vascular surgery involving prosthetic material and they reported that no differences were found between teicoplanin and cefalosporins with respect to the development of surgery site infections.[33]

The third antibiotic applied in the present study was vancomycin, and it also decreased bacterial counts. The most effective protocol was the three-dose regimen and for all regimens the efficacy was greater than that of cefazoline. In a study by Maki *et al.*, three-hundred twenty-one adults undergoing cardiac or major vascular operations were randomized to receive intravenous cefazolin, cefamandole or vancomycin for prophylaxis against surgical infection in a double-blind trial. They concluded that administration of vancomycin (approximately 15 mg/kg), immediately preoperatively, resulting in protection against postoperative infection superior to that obtained with cefazolin or cefamandole. As a result of their study, they have claimed that vancomycin deserves consideration for inclusion in the prophylactic regimen (1) for prosthetic valve replacement and prosthetic vascular graft implantation, to reduce the risk of implant infection by methicillin-resistant coagulase-negative staphylococci and enterococci; (2) for any cardiovascular operation if the patient has recently received broad-spectrum antimicrobial therapy; and (3) for all cardiovascular operations in centers with a high prevalence of surgical infection with methicillin-resistant staphylococci or enterococci.[34]

In the present study, a comparison between teicoplanin and vancomycin revealed that teicoplanin is more effective than vancomycin. In a recent study, Pea *et al.* reported that in patients undergoing major vascular surgery a single 800 mg preoperative teicoplanin dose may be considered effective in ensuring plasma levels >10 mg/L at the time of wound closure even in cases of very long-lasting operations, with no need for intraoperative re-dosing. They found that teicoplanin may present two practical advantages compared with vancomycin in the handling of antimicrobial prophylaxis during elective surgery.

First, unlike vancomycin, which has to be slowly infused in 1–2 h prevent the 'red man' syndrome, teicoplanin may be administered as an intravenous bolus, enabling timely during induction of anaesthesia in the operating room. Second, the lack of a need for intraoperative re-dosing even in long-lasting operations makes teicoplanin easier to use than vancomycin.[35]

According to our results, the most feasible antibiotic in terms of preventing vascular graft infections seems to be teicoplanin. Vancomycin is also superior to cefazolin. In addition, a three days regimen applied perioperatively may be more useful for all antibiotics. In general, teicoplanin is associated with a lower incidence of adverse events, particularly nephrotoxicity and 'red man' syndrome, than vancomycin. The lack of toxicity renders routine serum monitoring of teicoplanin unnecessary, even when it is co-administered with an aminoglycoside. However, a lower rate of toxicity and lack of routine assay costs make teicoplanin an attractive and cost-effective option for treating infections where the agents have similar efficacy, even when acquisition costs are greater than those for vancomycin.[36]

Our animal model used in the present study may not be directly comparable with graft implantation into a blood vessel, and caution is needed to compare these results with the real situation of an implanted graft in the arteries of a living human being. Prophylaxis in vascular surgery must be assessed in well-designed case-control studies, their cost-effectiveness must be established, and staphylococcal resistance must be monitored closely. However, the results of this study demonstrated that the use of teicoplanin, vancomycin and cefazoline for perioperative prophylaxis in all regimens tested may prevent bacterial growth.

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