Eur J Vasc Endovasc Surg **31**, 274–279 (2006)
doi:10.1016/j.ejvs.2005.09.018, available online at http://www.sciencedirect.com on SCIENCE DIRECT®

Efficacy of Vancomycin, Teicoplanin and Fusidic Acid as Prophylactic Agents in Prevention of Vascular Graft Infection: An Experimental Study in Rat

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Objectives. *To compare the efficacy of a single prophylactic dose of intra-peritoneal vancomycin and teicoplanin with antibiotic treated Dacron grafts (vancomycin, teicoplanin, 10 or 40% fusidic acid-soaked grafts) in preventing vascular graft infections in a rat model.*
Design. *Prospective, randomized, controlled animal study.*
Materials and methods. *The graft infections were established in the subcutaneous tissues of 80 female Sprague–Dawley rats by the implantation of Dacron prostheses followed by the topical inoculation with methicillin-resistant Staphylococcus aureus. The study groups were as follows: (1) uncontaminated control group, (2) untreated contaminated group, (3) contaminated group with intra-peritoneal vancomycin, (4) contaminated group with intra-peritoneal teicoplanin, (5) contaminated group received vancomycin-soaked Dacron graft, (6) contaminated group received teicoplanin-soaked Dacron graft, (7) contaminated group received 40% fusidic acid-soaked Dacron graft, and (8) contaminated group received 10% fusidic acid-soaked Dacron graft prophylaxis. The grafts were removed after 7 days and evaluated by a quantitative culture analysis.*
Results. *No infection was detected in controls. The untreated contaminated group had a high bacteria count (6.0×10^4 CFU/cm^2 Dacron graft). Groups that received intra-peritoneal vancomycin or teicoplanin had less bacterial growth (4.8×10^3 and 3.9×10^3 CFU/cm^2 Dacron graft, respectively). Similarly, the group that received 10% fusidic acid-soaked graft showed less bacterial growth (3.6×10^3 CFU/cm^2 Dacron graft). The groups with vancomycin-, teicoplanin- and 40% fusidic acid-soaked grafts showed no evidence of infection. Statistical analyses demonstrated that intra-peritoneal prophylactic antibiotic treatment was less effective in inhibiting bacterial growth than high concentration antimicrobial-soaking of grafts.*
Conclusion. *The use of vancomycin-, teicoplanin- and 40% fusidic acid-soaked grafts was effective in preventing primary prosthetic vascular graft infection.*

Keywords: Vascular graft infection; Antibiotic prophylaxis; Rat model; Vancomycin; Teicoplanin; fusidic acid.

Introduction

The infection of vascular prosthetic grafts is a relatively uncommon phenomenon, with a reported incidence of between 0.5 and 8%.[1–9] The infection rate depends on the site of the reconstruction and the graft material used.[4] The incidence probably has been reduced by perioperative systemic antibiotic prophylaxis, shorter duration of procedures and minimization of blood loss, but the overall prevalence is increasing in parallel with the expansion in vascular reconstructive surgery.[4,10] Although new antimicrobial compounds are being used for prevention, vascular graft infection is still one of the most feared complications. It frequently results in prolonged hospitalization, organ failure, amputation and death. Mortality and amputation rates have been reported to be as high as 12–75 and 19–79%, respectively.[1,4,7,11]

The mechanism(s) of graft infection may be perioperative contamination, postoperative wound infection or systemic bacteraemia. The usual time for the entry of microorganisms is at operation; although they may be blood-born or lymphatic in origin, the probability of their presence in the arterial wall cannot be excluded.[1–5,8,9] The most frequent source of infection is staphylococci deriving from the patient's

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1078–5884/000274 + 06 $35.00/0

skin. Other potential sites include the urinary tract, intravascular loci, lung and pleural space, peritoneal cavity and finally surgical sites including prosthetic devices.[12] Prevention of these infections would have an important impact on patient mortality and the cost effectiveness of hospital care.[13] The mainstays of prophylaxis are asepsis and peri-operative administration of systemic antibiotics.[3,13–15] The choice of antibiotics and the length of the treatment are controversial although the first and second generation cephalosporins have been the most commonly used drugs.[2,12–14,16] However, after initial success, resistance to these drugs began to emerge. In particular, the widespread use of several antimicrobial agents, either in therapeutic or prophylactic regimens, resulted in a dramatic increase in the prevalence of multi-drug-resistant organisms, such as methicillin-resistant staphylococci.

In earlier reports, *Staphylococcus epidermidis* was found to be the most frequent cause of vascular graft infections, however, methicillin-resistant *Staphylococcus aureus* (MRSA) recently was reported to be the most common organism isolated in vascular graft infections.[2,3,5,10,11,14–18] MRSA graft infections were not associated with an increased risk of death but were associated with a significant increase in the risk of amputation and prolonged duration of hospitality.[3,17]

Despite the use of systemic antibiotic prophylaxis, vascular graft infections still occur. For this reason, antibiotic- and antimicrobial-impregnated grafts have recently been used in the several experimental and clinical studies for the prevention of vascular graft infections.[2,6,7,12–15,19–21] These grafts have been shown to be highly resistant to bacterial contamination and proposed as adjunctive prophylaxis.[2,12,14,15,20] In clinical studies, rifampin-impregnated Dacron grafts have been used for prevention of vascular graft infection. Other antibiotic-bonded grafts have only been used in experimental studies, not in clinical studies.

In clinical settings, glycopeptide antibiotics are in widespread use for the treatment of vascular graft infection, although they are not used for routine prophylaxis of vascular graft infection. If there is a risk of MRSA infection, glycopeptides may be used to prevent vascular graft infection. To date, there has been no study evaluating the use and comparison of intra-peritoneal and topical glycopeptides for the prevention of vascular graft infection. Therefore, we investigated the efficacy of topical and intra-peritoneal vancomycin and teicoplanin, as well as topical fusidic acid to prevent MRSA vascular graft infection in a rat model.

Material and Methods

Organisms

The strain of methicillin-resistant *S. aureus* used in this study was isolated from a clinical specimen submitted for routine bacteriological investigation to the Department of Microbiology, Faculty of Medicine, Kahramanmaras Sutcu Imam University, Turkey. Commercially available *S. aureus* ATCC 25923 was used as a control in susceptibility testing.

Drugs

Vancomycin (Vankomisin HCI), teicoplanin (Targocid) and fusidic acid (Fucidin krem 2%) were obtained from Abbott Laboratories (Istanbul, Turkey), Aventis Pharma (Istanbul, Turkey) and Abdi Ibrahim Drug Company (Istanbul, Turkey), respectively. Fusidic acid prepared as 10 and 40% was dissolved in 100 cm^3 ClinOleic 20% (Eczacıbaşı-Baxter, Istanbul, Turkey).

Susceptibility testing

The antimicrobial susceptibilities of two MRSA strains were determined by using the micro-broth dilution method, according to the procedures outlined by the National Committee for Clinical Laboratory Standards. The minimum inhibition concentration was taken to be the lowest antibiotic concentration at which observable growth was inhibited. Experiments were performed in triplicate.

Rat model

The study was approved by the Ethics Committee of Faculty of Medicine, Kahramanmaras Sutcu Imam University, Turkey. Adult female Sprague–Dawley rats (weight range, 200–250 g) were studied. All rats had free access to standard rat chow and tap water. The study included a control group with no graft contamination and no antibiotic prophylaxis (group 1), one contaminated group that did not receive any antibiotic prophylaxis (group 2), one contaminated group that received peri-operative 10 mg/kg intra-peritoneal vancomycin (group 3), one contaminated group that received peri-operative 10 mg/kg intra-peritoneal teicoplanin (group 4), four contaminated groups that separately received vancomycin-, teicoplanin-, fusidic acid 10%- and fusidic acid 40%-soaked grafts (group 5, 6, 7 and 8, respectively). Each group consisted of 10 animals.

Rats were anesthetized with intra-peritoneal ketamine (10 mg/kg) and xylazine (3 mg/kg), the backs 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. Prior to implantation, the Dacron graft segments were impregnated with 50 mg/L vancomycin (group 5), 50 mg/L teicoplanin (group 6), 10% fusidic acid (group 7) and 40% fusidic acid (group 8). Antibiotic soaking was done immediately before implantation by placing the grafts for 20 min in a sterile solution of the relevant agent. Biochemical assessment of antibiotic binding to soaked graft was not performed.The pockets were closed by 5/0 polypropylene sutures (Dogsan, Turkey), and a sterile saline solution (1 mL) containing the MRSA strain at a concentration of 2×10^7 CFU/mL was inoculated onto the graft surface 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. At this stage, to investigate the existence of an infection blood samples were collected for the culture analysis.

Assessment of the infection

The explanted grafts were placed in sterile tubes, 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 to minimize the carryover effect 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 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 for all groups are presented as mean$\pm$standard deviation and statistical comparisons between groups were performed using analysis of variance (ANOVA) on the log-transformed data with differences between groups assessed with Turkey significant difference test. Statistical significance was defined as a p value of <0.05.

Results

None of the animals included in the uncontaminated control group (group 1) had either anatomic or microbiological evidence of graft infection. In contrast, all rats in the contaminated group that did not receive any antibiotic prophylaxis (group 2) demonstrated graft infections, evidenced by the quantitative culture results showing $6\times10^4\pm2\times10^4$ CFU/cm^2 graft within local signs of perigraft inflammation, $p<0.001$ *versus* group 1. The intra-peritoneal vancomycin treated group (group 3) had less bacterial growth, $4.8\times10^3\pm1.8\times10^3$ CFU/cm^2 graft, but without local signs of perigraft inflammation, $p<0.002$ and $p<0.001$ *versus* groups 1 and 2 respectively. Similarly, the intra-peritoneal teicoplanin treated group (group 4) had less bacterial growth, $3.9\times10^3\pm2.6\times10^2$ CFU/cm^2 graft without local signs of perigraft inflammation, $p<0.001$ *versus* groups 1 and 2. The groups with vancomycin- and teicoplanin-soaked Dacron graft (group 5 and 6) showed no evidence of staphylococcal infection with negative quantitative cultures, both $p<0.003$ *versus* unsoaked graft and same antibiotic given intra-peritoneally. For group 7, where 10% fusidic acid soaked -Dacron graft was used, there was low bacterial growth ($3.6\times10^3\pm2.2\times10^3$), whilst in group 8, with 40% fusidic acid soaked grafts, there was no evidence of graft infection ($p<0.001$). While the bacterial growth of group 7 was significantly lower than those of group 1, 5 and 6 ($p<0.001$), it was similar with those of group 3 and 4. The results are summarized in Table 1.

Blood cultures were negative in all rats. Finally, none of the animals included in any group died or had clinical evidence of drug-related adverse effects, such as anorexia, vomiting, diarrhea, or other symptoms.

Discussion

The widespread use of several antimicrobial agents in both therapeutic and prophylactic regimens has resulted in a significant increase in the prevalence of multi-drug-resistant organisms, such as MRSA. The short doubling times and genetic plasticity of bacteria permit these organism to rapidly prove specific mutations for their ability to enhance growth in inhospitable environments. Mutations conferring resistance help bacteria to survive attach from antibiotics used clinically.[14,16] Graft infection with

Table 1. Quantitative microbiological results of in vivo experiments

Group	Method of prophylaxis	Quantitative graft culture (CFU/cm^2)
1	–	0
2	–	$6.0\times10^4\pm2.0\times10^4$ *
3	Intra-peritoneal vancomycin (10 mg/kg)	$4.8\times10^3\pm1.8\times10^3$ *,†
4	Intra-peritoneal teicoplanin (10 mg/kg)	$3.9\times10^3\pm2.6\times10^2$ *,†
5	Vancomycin-soaked graft (50 mg/L)	0†,‡,§
6	Teicoplanin-soaked graft (50 mg/L)	0†,‡,§
7	Fusidic acid-soaked graft (10%)	$3.6\times10^3\pm2.2\times10^3$ *,†,¶,‖
8	Fusidic acid-soaked graft (40%)	0†,‡,§,**

Each group consisted of 10 animals and statistical significance was evaluated by the use analysis of variance (ANOVA) on the log-transformed data by the Turkey significant difference test.
* Statistically significant versus group 1.
† Statistically significant versus group 2.
‡ Statistically significant versus group 3.
§ Statistically significant versus group 4.
¶ Statistically significant versus group 5.
‖ Statistically significant versus group 6.
** Statistically significant versus group 7.

MRSA has emerged as a significant problem among hospitalized patients. The emergence of the resistant organisms has stimulated research for new antimicrobial drugs and biomaterials. The development of vascular prostheses resistant to infection has considerable appeal, but as yet, none are commercially available. For vascular grafts, antimicrobials bounded at high concentrations to prosthetic grafts have been proposed as adjunctive prophylaxis, with encouraging results.[2,12,14–16,20,21] One focus has been the development of a bacterial resistant vascular prosthesis through binding of an antibiotic to Dacron grafts, with impregnated collagen or gelatin matrix as the release system. Such antibiotic-impregnated grafts have been shown to be highly resistant to bacterial contamination in animal models.

Rifampin-soaked Dacron grafts have been used successfully. Nevertheless, the development of the rifampicin-resistance would be a major drawback to the wide-spread use of such a graft and emphasizes the need for further prophylactic approaches.[16] We compared the efficacy of systemic vancomycin and teicoplanin prophylaxis with antibiotic (vancomycin, teicoplanin or fusidic acid) soaked Dacron grafts in a MRSA vascular graft infection model. Resistance to these antibiotics is uncommon and they show activity against clinically important staphylococci. These features were the main reasons of preferring these agents in the present study. The glycopeptides, vancomycin and teicoplanin, are bactericidal agents with the ability to inhibit bacterial cell wall synthesis. Teicoplanin is preferable to vancomycin, since it has fewer side-effects, e.g. nephrotoxicity and ototoxicity, and therapeutic drug monitoring is usually unnecessary.[3,22] Fusidic acid is a topical antibiotic that has an effective narrow-spectrum antibiotic for the treatment of gram-positive bacteria including MRSA and inhibits bacterial protein synthesis. It is used for the treatment of superficial skin infection due to *S. aureus*. Fusidic acid is active against most MRSA strains because of its wide tissue distribution, high tolerability, lack of cross-resistance with β lactam antibiotics and good antimicrobial activity against *S. aureus* (including MRSA).[18,22] We chose Dacron in this study as many investigators due to its less resistance to bacterial adherence than polytetrafluoroethylene.[15] However, we did not assess anti-biotic binding to the Dacron grafts, which is a limitation of the present study.

Our study examining the primary prevention of vascular graft infection with vancomycin- and teicoplanin-soaked grafts has shown these antibiotics to be effective. For primary prevention of vascular graft infection, single doses of intra-peritoneal vancomycin and teicoplanin appear less effective than vancomycin- and teicoplanin-soaked grafts. Perhaps a single parenteral dose of antibiotic was insufficient for prevention of prosthetic vascular graft infection. No bacterial growth was detected on the vancomycin- and teicoplanin-soaked Dacron grafts. Although Giacometti *et al.* found that graft infection with multiple-drug-resistant *S. epidermidis* in a rat model was higher in vancomycin- and teicoplanin-coated Dacron grafts than in those coated with polycationic peptides (ranalexin and bufforin), the microorganism they used already had intermediate resistance to glycopeptide antibiotics.[15] They also investigated the efficacies of polycationic peptides, ranalexin and bufforin, in the rat model, and compared these peptides-soaked grafts with rifampin-soaked graft and intra-peritoneal cefazolin

prophylaxis.[14] They found that the efficacies of the polycationic peptides against the methicillin-susceptible and methicillin-resistant *S. epidermidis* strains were not significantly different from that of rifampin.[14] Vicaretti and colleagues established a *S. epidermidis* vascular graft infection model in sheep and suggested that an increased concentration of rifampin bound to Dacron grafts significantly reduced the incidence of prosthetic vascular graft infection following a challenge of drug-resistant staphylococci.[5] Numerous other models, with different microorganisms, antibiotics and regimens have been reported. However, there is little evidence for the use of fusidic acid.

We investigated the *in vivo* efficacy of two different concentrations of fusidic acid spontaneously bound to gelatin-sealed Dacron graft, in the prevention of *S. aureus* infection. Our experiments demonstrated that 40% fusidic acid was considerably more effective than 10% fusidic acid. Forty percent fusidic acid completely inhibited bacterial growth of MRSA strains even though multi-resistant organisms were topically inoculated on the Dacron prosthesis. There was no evidence of fusidic acid toxicity in our study. Ghiselli *et al.* investigated another topical antibiotic mupirocin and reported mupirocin-soaked graft to be more effective than rifampin-soaked graft against MRSA.[16] Giacometti and colleagues investigated mupirocin-bound Dacron grafts for preventing infection of the graft in a rat model and showed that mupirocin was more effective than vancomycin against *S. aureus*.[20] In view of these results, the optimal management for prevention of vascular graft infection remains controversial. However, the use of antibiotic-impregnated prosthetic grafts may become an important future consideration for chemoprophylaxis in vascular surgery.

In conclusion, vancomycin, teicoplanin and 40% fusidic acid treatment of Dacron grafts is effective in preventing primary graft infection in an experimental model. Our experience with antibiotic-soaked grafts in the management of vascular graft infections suggest that this technique seems to be a useful option for treating one of the most dreaded vascular complications. Indeed, new antimicrobial-coated grafts are future options for the development of protocols designed to prevent graft infection.

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Accepted 23 September 2005
Available online 15 December 2005