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Morbidity and mortality associated with arterial surgery site infections by resistant microorganisms

Morbimortalidade relacionada às infecções de ferida operatória ocasionadas por micro-organismos resistentes em cirurgias arteriais

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Abstract

Background: Surgical site infection is a severe complication of peripheral vascular surgery with high morbidity and mortality rates. **Objective:** To evaluate the morbidity and mortality of infections of peripheral artery surgery sites caused by resistant microorganisms. **Methods:** This was a prospective study of a cohort of patients who underwent peripheral artery revascularization procedures and developed surgical site infections between March 2007 and March 2011. **Results:** Mean age was 63.7 years; males accounted for 64.3% of all cases. The overall prevalence of bacterial resistance to antimicrobials was 65.7%. The most common microorganism identified was *Staphylococcus aureus* (30%). Comparison of the demographic and surgical characteristics of both subsets (resistant versus non-resistant) detected a significant difference in length of preoperative hospital stay (9.3 days vs. 3.7 days). The subset of patients with infections by resistant microorganisms had higher rates of reoperation, lower numbers of limb amputations and lower mortality, but the differences compared to the subset without resistant infections were not significant. Long-term survival was similar. **Conclusions:** This study detected no statistically significant differences in morbidity or mortality between subsets with surgical wound infections caused by resistant and not-resistant microorganisms.

Keywords: surgical wound infection; drug resistance; surgery.

Resumo

Contexto: A infecção de ferida operatória é uma complicação grave da cirurgia vascular periférica e está associada a elevadas taxas de morbidade e mortalidade. **Objetivo:** Avaliar a morbidade e a mortalidade relacionadas às infecções de ferida operatória causadas por micro-organismos resistentes em cirurgias arteriais periféricas. **Métodos:** Coorte prospectiva envolvendo pacientes submetidos a procedimentos de revascularização arterial periférica que desenvolveram infecção de sítio cirúrgico, entre março de 2007 e março de 2011. **Resultados:** A média de idade desses pacientes foi de 63,7 anos; homens representaram 64,3% de todos os casos. A prevalência total de resistência bacteriana foi de 65,7%. O micro-organismo mais isolado foi o *Staphylococcus aureus* (30%). Comparando-se as características demográficas e cirúrgicas das duas amostras (com e sem resistência), foi demonstrado que o tempo de permanência hospitalar apresentou diferença significativa (9,3 dias × 3,7 dias). O grupo de pacientes portadores de infecção por micro-organismo resistente apresentou elevadas taxas de reoperação, amputação de membro inferior e mortalidade, porém sem diferença estatística quando comparado ao grupo sem resistência. No longo prazo, a sobrevida foi similar. **Conclusão:** este estudo não demonstrou diferença estatística quanto a morbidade e mortalidade entre os grupos com infecção de ferida operatória ocasionada por micro-organismos resistentes e não resistentes.

Palavras-chave: infecção de ferida operatória; resistência medicamentosa; cirurgia.

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INTRODUCTION

Surgical site infection is a severe complication of peripheral vascular surgery. Surgical site infection occurs in 0.9-22% of arterial vascular surgeries, and recent series have reported rates of around 3%.[1,2] Deep infection with involvement of the wall of the operated artery or the implanted graft occurs in 1.2-13% of arterial surgeries.[2,3] França et al. reported a 4.6% incidence of synthetic graft infection in peripheral vascular surgery.[2] This type of infection is more frequent in emergency surgeries and inguinal dissections and when vascular grafts are used in the femoral region or via a subcutaneous route. Treatment is complex, involving reoperation, use of wide-spectrum antimicrobials and extended hospital stays, resulting in high mortality (10-76%) and morbidity rates (8-53%).[2-5]

The microorganisms most frequently involved in surgical site infections are *Staphylococcus aureus* and Coagulase-negative *Staphylococcus*.[5-7] Later infections are often caused by Coagulase-negative *Staphylococcus*. Gram-negative bacterial infections are very destructive and are often caused by *Pseudomonas aeruginosa*.[8,9]

The recent occurrence of resistant strains has raised new concerns about antimicrobial prophylaxis and treatment and morbidity and mortality rates. Methicillin-resistant *Staphylococcus aureus* (MRSA) is currently the most frequently isolated pathogen in complex and severe infections related to vascular surgery.[6] Prolonged prophylaxis and indiscriminate use of antimicrobials contributed to the development of bacterial resistance.[7,10] In turn, the increased incidence of multi-resistant pathogens in vascular surgeries contributes to increased morbidity and mortality rates.[6,9,11,12] However, some authors found that no increase in morbidity[13] or mortality was associated with MRSA infections.[14]

This study was conducted with the aim of determining the impact of bacterial resistance to antibiotics on morbidity and mortality from surgical site infections after peripheral artery surgery.

METHODS

This was a cohort study of patients who underwent peripheral artery revascularization surgery from March 2007 to March 2011 and who developed surgical site infections during the postoperative period. Sample selection was consecutive. Demographic data, comorbid conditions, surgical details, microbiology and characteristics of wound infection and hospital stay were reviewed. Presence or absence of bacterial resistance to antibiotics was used to stratify the sample. Data on readmissions and repeat operations during the follow-up period were also recorded. The primary outcome was mortality; secondary outcomes were reoperation, graft excision and lower limb amputation. Patients who were subjected to limb revascularization procedures had critical limb ischemia. This study was approved by the ISCMPA ethics committee.

Bacterioscopic examination, cultures and antimicrobial susceptibility tests were conducted for all cases. The material collected comprised surgical site secretions, tissues or graft fragments (if affected) with clinical diagnoses of infection. All material was collected by the same researcher and analyzed by the same laboratory, following Clinical and Laboratory Standards Institute procedures.[15] Polymicrobial samples and samples with negative culture results were excluded from the study. Patients with negative cultures were also excluded from the study. All patients in this study received a prophylactic antibiotic prior to skin incision (cephalosporin).

Bacterial resistance to antimicrobials was defined as follows: *Staphylococcus aureus* - resistance to oxacillin (all beta-lactams), Coagulase-negative Staphylococcus - resistance to oxacillin (all beta-lactams), *Klebsiella pneumoniae*, *Enterobacter, Escherichia coli* and *Proteus mirabilis* - resistance to amikacin, ceftriaxone, cefepime or ciprofloxacin, *Pseudomonas aeruginosa* - resistance to imipenem or only sensitivity to imipenem but resistant to other antimicrobials, *Enterococcus feacalis* - resistance to vancomycin or teicoplanin, and *Streptococcus viridans* - resistance to penicillin.

Comparisons of the results for quantitative variables were performed using Student's *t* test and the Mann Whitney test. Categorical variables were compared using chi-square tests and Fisher's exact test. Symmetry of data distribution was evaluated using the Kolmogorov-Smirnov test (P<.10). For survival analysis, the Kaplan-Meier method was used to identify major factors associated with mortality and then we constructed a Cox multiple regression model (Wald method) with death as the dependent variable. Variables with significant or borderline (P<.10) differences according to the bivariate analysis were included in this model. Statistical tests with a two-tailed p-value < .05 were considered significant. Analyses were performed using SPSS 17 (Statistical Package for Social Sciences) from SPSS Inc, Chicago, IL.

RESULTS

Baseline characteristics

During the study period, seven hundred patients were treated at our department using peripheral artery surgery. Twenty patients with polymicrobial and negative cultures were excluded from the study. Data from seventy patients who developed surgical site infection after peripheral artery surgery were analyzed during the study, stratified into two subsets: those infected by resistant bacteria and those infected by non-resistant bacteria. The patients' mean age was 63.7 years, and males predominated (64.3%). Patients' demographic data and differences between subsets are summarized in Table 1. No significant differences in demographic characteristics between the two subsets were detected. Mean preoperative hospital stay was significantly longer for patients with infection due to resistant microorganisms (P=0.001). No significant differences between groups were detected for the variables use of therapeutic antimicrobials, graft implantation, type of surgery or *Szilagyi*[16] classification. The principal surgical characteristics are shown in Table 1.

Microbiology

The most frequent microorganism isolated from surgical site infections was *Staphylococcus aureus*, present in 30% of all cases and the most prevalent bacteria in both subsets. Overall prevalence of bacterial resistance to antimicrobials was 65.7%. Infections due to Coagulase-negative *Staphylococcus* and *Escherichia coli* were significantly more common (P=0.001) in the group with non-resistant bacteria; whereas infection due to *Enterobacter* was statistically more common (P=0.001) in the group with resistant bacteria. Table 2 lists all of the microbiological analysis results.

Morbidity and mortality

The group of patients with resistant surgical site infections exhibited higher rates of repeat surgery,

Table 1. Demographic and surgical characteristics of patients with surgery wound infections.

Characteristics	Total (n=70)	Non-resistant (n=24)	Resistant (n=46)	P
Age, years±SD	63.7±8.8	65.1±10.7	62.9±7.6	0.234
Males, n (%)	45 (64.3)	14 (58.3)	31 (67.4)	0.626
Comorbidities, n (%)				
Smoking	59 (84.3)	19 (79.2)	40 (87.0)	0.493
Hypertension	50 (71.4)	19 (79.2)	31 (67.4)	0.406
Coronary artery disease	27 (38.6)	8 (33.3)	19 (41.3)	0.609
Diabetes mellitus	28 (40.0)	10 (41.7)	18 (39.1)	1.000
Obesity (BMI>30)	14 (20.0)	6 (25.0)	8 (17.4)	0.534
Therapeutic preop. antibiotics, n (%)	19 (27.1)	6 (25.0)	13 (28.3)	1.000
Preoperative stay, days±SD (Me)	7.4±8.2 (5.0)	3.7±4.2 (2.5)	9.3±9.1 (7.0)	0.001
Type of surgery, n (%)				0.114
Femoropopliteal	29 (41.4)	10 (41.7)	19 (41.3)	
Aortobifemoral	16 (22.9)	3 (12.5)	13 (28.3)	
Distal revascularization	6 (8.6)	2 (8.3)	4 (8.7)	
Axilobifemoral	8 (11.4)	4 (16.7)	4 (8.7)	
Iliofemoral crossover	3 (4.3)	0 (0.0)	3 (6.5)	
Femorofemoral crossover	4 (5.7)	3 (12.5)	1 (2.2)	
Iliofemoral	2 (2.9)	2 (8.3)	0 (0.0)	
Aortoiliac	2 (2.9)	0 (0.0)	2 (4.3)	
Use of graft, n (%)	54 (77.1)	21 (87.5)	33 (71.7)	0.234
Topography of infection, n (%)				0.401
Inguinal	49 (70.0)	17 (70.8)	32 (69.6)	
Lower limb	16 (22.9)	4 (16.7)	12 (26.1)	
Abdomen	5 (7.1)	3 (12.5)	2 (4.3)	
Classification of infection, n (%)				0.624
Superficial	20 (28.6)	9 (37.5)	11 (23.9)	
Incisional	36 (51.4)	10 (41.7)	26 (56.5)	
Incisional with graft exposure	14 (20.0)	5 (20.8)	9 (19.5)	

Me: Median, concentration of 50% of the sample with values less than or equal to the median.

but lower rates of limb amputation and mortality, although the differences were not significant. These data are summarized in Table 3. Multivariate analysis (logistic regression) of parameters that were statistically significant in bivariate analyses did not detect significant associations with death (P>0.05).

One-year survival rates for the non-resistant and resistant subsets were 87.9% and 79.7% respectively and 5-year survival rates were 65.9% and 47.6% respectively. Analysis of Kaplan-Meier curves did not detect significant differences between the subsets with and without resistant bacteria (Mantel-Cox log rank test = 0.206, P=0.652). There were therefore no statistically significant differences between mean time of survival estimates for the subsets with antimicrobial resistant (42.7 months ± 3.2 days) and non-resistant (48.7 months ± 6.6 days) pathogens (Figure 1).

DISCUSSION

Resistant bacterial strains raise new concerns about antimicrobial prophylaxis and treatment and morbidity and mortality rates within the context of peripheral vascular surgery.[17] The importance of bacteria that are resistant to antibiotics lies in the fact that they have become much more prevalent in hospitals,[18,19] reducing the efficacy of antimicrobial treatments,[20] disseminating resistance,[21] increasing medical costs[22] and raising morbidity and mortality rates among surgery patients.[6,9,11,12]

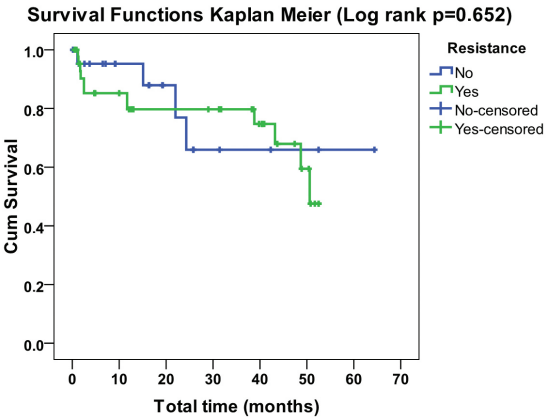

Figure 1. Survival curve (Kaplan-Meier) for patients with resistant infections and non-resistant infections.

Table 2. Distribution of organisms isolated from surgical wound infections in vascular patients.

Microorganism	Total n (%)	Non-resistant n (%)	Resistant n (%)	P
				0.001
Staphylococcus aureus	21 (30)	6 (25.0)	15 (32.6)	
Coagulase-negative *Staphylococcus*	20 (28.6)	12 (50.0)	8 (17.4)	
Klebsiella pneumoniae	8 (11.4)	0	8 (17.4)	
Enterobacter sp.	7 (10)	0	7 (15.2)	
Pseudomonas aeruginosa	5 (7.1)	1 (4.2)	4 (8.7)	
Escherichia coli	4 (5.7)	3 (12.5)	1 (2.2)	
Proteus mirabilis	3 (4.3)	0	3 (6.5)	
Streptococcus viridans	1 (1.4)	1 (4.2)	0	
Enterococcus feacalis	1 (1.4)	1 (4.2)	0	
TOTAL	70	24	46	

Table 3. Analysis of primary and secondary outcomes (mortality and morbidity) for patients with resistant and non-resistant bacterial infections.

Characteristics	Totals n (%)	Non-resistant n (%)	Resistant n (%)	P
Reoperation, n (%)	62 (88.6)	19 (79.2)	43 (93.5)	0.164
Lower limb amputation, n (%)	33 (47.1)	9 (37.5)	24 (52.2)	0.360
Excision of graft, n (%)	25 (35.7)	12 (50.0)	13 (28.3)	0.124
Mortality, n (%)	14 (20.0)	4 (16.7)	10 (21.7)	1.000
Overall	9 (64.3)	3 (75.0)	6 (60.0)	
Specific (related to infection)	5 (35.7)	1 (25.0)	4 (40.0)	
Postoperative mortality, n (%)				0.534
Early	7 (10.0)	1 (4.2)	6 (13.0)	
Late	7 (10.0)	3 (12.5)	4 (8.7)	
TOTAL	70	24	46	

The main factors involved in development of surgical site infections are graft implantation, local complications, age, comorbidities,[23-28] grafts in extra-anatomical positions, prolonged preoperative hospital stays, emergency surgery, extended periods in surgery, concomitant gastrointestinal surgery and arterial reoperation.[3,29] In this study, patients had a high mean age, were predominantly male and all had comorbidities, most of which were multiple, which are typical characteristics of patients undergoing peripheral artery surgery. Patients who developed infections caused by resistant microorganisms had longer preoperative hospital stays, which the literature shows can be related to increased infection rates and the prevalence of resistant bacteria.[30] One explanation for this long preoperative stay could be difficulties with availability of hospital beds and the need to conduct extensive investigations before the revascularization procedure. Other baseline characteristics were similar for both subsets in this study.

Staphylococcus aureus, Coagulase-negative *Staphylococcus*, *Pseudomonas*, *Escherichia coli*, *Enterobacter* and *Proteus* are commonly isolated from surgical site infections[5,6,9] Overall, the most common pathogen is *Staphylococcus aureus* (33-55%).[7] Cowie et al. found that MRSA was the second most frequent microorganism (21%) isolated from infections in patients submitted to vascular surgery.[11] The most prevalent microorganism causing infection in our study was *Staphylococcus aureus* (30%), followed by Coagulase-negative *Staphylococcus* (28.6%). Many authors report that Coagulase-negative *Staphylococcus* is one of the microorganisms most often responsible for hospital infections[14] and especially so with relation to surgical site infections after vascular surgery.[5,6,9,31-36] It is also associated with high rates of antimicrobial resistance.[32,34] Our data confirmed a high prevalence of Coagulase-negative *Staphylococcus* (28.6% overall), but this pathogen was significantly more prevalent among the non-resistant group (50% vs. 17.4%).

Many authors agree that the increased incidence of multi-resistant pathogens and more aggressive strains in vascular surgery infections contributes to high rates of morbidity and mortality,[6,9,11,12] with mortality rates of up to 75% reported.[6,9] High rates of amputation (40%) and prosthesis excision (11.5%) and longer duration hospital stays are reported when patients are develop surgical site infections that have resistance.[12] Cowie et al. showed that MRSA infections in patients undergoing vascular procedures increased the risk of mortality and clinical complications, including the need for hospitalization in the intensive care unit, repeated hospitalizations and interventions, and longer hospitalization.[11] A study conducted by Taylor et al. showed that infections caused by *Staphylococcus aureus* resistant to beta-lactam antibiotics are associated with high morbidity rates, longer hospital stays (29.6 days vs. 22.7 days), higher rates of lower limb amputation (40%) and a greater probability that an infected graft will have to be removed (7.7%).[12] However, some authors found no increase in morbidity[13] or mortality associated with MRSA infection.[14]

In our study, patients with resistant surgical wound infections had higher rates of repeat surgeries, and lower limb amputation and mortality; but these results were not statistically significant. On the other hand, the group with non-resistant infections had a high rate of graft excision, which was probably associated with early and aggressive treatment. Multivariate analysis showed that mortality was not associated with bacterial resistance, after adjustment of baseline factors. Patients with non-resistant infections had higher survival rates after one-year and five-year follow-up, but this result also failed to attain significance. Long-term survival was statistically similar for both subsets. This finding could be due to the multiple comorbidities, advanced diseases and high cardiovascular risk levels of these patients. These results shows that vascular surgery patients with resistant surgical site infections may suffer worse outcomes, especially over the short-term follow-up period, irrespective of correct management and care, with high rates of complications and death.

Study limitations include the sample size, lack of uniformity in the infection samples collected, exclusion of cases with polymicrobial infections and with negative cultures, and the sample drawn from a specific and limited population, consisting of patients with multiple advanced diseases who face barriers to access of appropriate medical support. It is probable that statistical analysis of a larger sample could detect more significant results.

This study detected no statistical differences in morbidity or mortality between a subset of patients with surgical wound infections caused by resistant microorganisms and another with non-resistant infections. Patient follow-up revealed a trend towards poorer outcomes among patients with resistant infections, but over the long term survival was similar in both subsets.

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