J Infect Chemother xxx (2018) 1–8

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: http://www.elsevier.com/locate/jic

Original Article

Gentamicin may have no effect on mortality of staphylococcal prosthetic valve endocarditis☆

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ARTICLE INFO

Article history:
Received 30 August 2017
Received in revised form
23 January 2018
Accepted 6 March 2018
Available online xxx

Keywords:
Endocarditis
Heart valve prosthesis
Staphylococcus
Staphylococcus aureus

ABSTRACT

Purpose: To analyze the influence of adding gentamicin to a regimen consisting of β-lactam or vancomycin plus rifampicin on survival in patients suffering from Staphylococcal prosthetic valve endocarditis (SPVE).

Methods: From January 2008 to September 2016, 334 patients with definite SPVE were attended in the participating hospitals. Ninety-four patients (28.1%) received treatment based on β-lactam or vancomycin plus rifampicin and were included in the study. Variables were analyzed which related to patient survival during admission, including having received treatment with gentamicin.

Results: Seventy-seven (81.9%) were treated with cloxacillin (or vancomycin) plus rifampicin plus gentamicin, and 17 patients (18.1%) received the same regimen without gentamicin. The causative microorganism was *Staphylococcus aureus* in 40 cases (42.6%) and coagulase-negative staphylococci in 54 cases (57.4%). Overall, 40 patients (42.6%) died during hospital admission, 33 patients (42.9%) in the

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https://doi.org/10.1016/j.jiac.2018.03.003

Gentamicin
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group receiving gentamicin and 7 patients in the group that did not (41.2%, P = 0.899). Worsening renal function was observed in 42 patients (54.5%) who received gentamicin and in 9 patients (52.9%) who did not (p = 0.904). Heart failure as a complication of endocarditis (OR: 4.58; CI 95%: 1.84–11.42) and not performing surgery when indicated (OR: 2.68; CI 95%: 1.03–6.94) increased mortality. Gentamicin administration remained unrelated to mortality (OR: 1.001; CI 95%: 0.29–3.38) in the multivariable analysis.

Conclusions: The addition of gentamicin to a regimen containing vancomycin or cloxacillin plus rifampicin in SPVE was not associated to better outcome.

1. Introduction

Prosthetic valve endocarditis (PVE) is the most serious complications related to heart valve replacement and is observed in 1–6% of the patients [1,2]. Staphylococcal PVE (SPVE) is characterized by higher mortality and complication rates [3].

To treat SPVE, the most relevant guidelines recommend combined treatment with vancomycin (initially 1 g/12 h, then to maintain trough blood levels of 15–20 μg/mL) an anti-staphylococcal β-lactam (cloxacillin2 g/4 h) plus rifampicin (300 mg/8 h) (6 weeks) plus gentamicin (3 mg/kg/24 h, 2 weeks) [4,5]. These recommendations are based on *in vitro* studies, animal models and observational cohorts [6–10]. Despite their general acceptance, in a high percentage of cases these recommendations are not followed, partly due to the risk of renal failure associated with the use of gentamicin and also on account of the belief that there are more effective antibiotics [11,12].

Moreover, recent studies in native valve *Staphylococcus aureus* IE have shown that gentamicin is not associated with improved prognosis when administered in combination with a β-lactam or a glycopeptide [13,14]. Removal of gentamicin from the recommended antibiotic regimen for SPVE could result in reduced renal toxicity without impairing patient survival. However, the impact of adding gentamicin to β-lactam/glycopeptide plus rifampicin in SPVE patients is unknown.

The purpose of the present study was to evaluate the impact of gentamicin administration on in-hospital mortality in SPVE.

2. Material and methods

From January 2008 to September 2016, 3467 consecutive patients with definite or possible IE, according to the modified Duke criteria [15], were prospectively included in the "Spanish Collaboration on Endocarditis – Grupo de Apoyo al Manejo de la Endocarditis infecciosa en España (GAMES)" registry maintained by 27 Spanish hospitals. Multidisciplinary teams completed standardized case report forms with IE episode and follow-up data that included clinical, microbiological and echocardiographic sections [16,17]. Regional and local ethics committees approved the study and all patients gave their informed consent.

Patients were included if they were treated with cloxacillin or vancomycin (as the main antibiotic) plus rifampicin with or without gentamicin. Patients were classified in the gentamicin group if they had received gentamicin for more than 48 h. Patients with SPVE treated with other antibiotics, such as daptomycin, fosfomycin or linezolid, for more than 48 h were excluded from the study. Eight hundred and nineteen patients presented definite PVE. Of these, 334 (40.8%) were caused by Staphylococci species. Ninety-four patients (28.1%) received a cloxacillin or vancomycin based antibiotic regimen [1]. Non- β-lactam antibiotics received by the remaining patients were daptomycin (76%), linezolid (34%) and fosfomycin (20%).

3. Definitions

Active IE was defined as endocarditis with at least one of the following: positive blood cultures, fever, leukocytosis, raised inflammation markers or current antibiotic treatment [17]. Microbiological diagnosis was determined by blood, valve cultures and/or by molecular techniques [17]. Transthoracic and transesophageal echocardiography were performed on patients with clinical or microbiological suspicion of IE according to international recommendations. The same protocol was implemented for the diagnosis of valve dysfunction and intracardiac complications: abscess, vegetation, pseudoaneurysm and fistula [18,19]. The EuroScore and LogEuroScore were used to assess surgical risk [20]. All the necessary variables were collected to calculate the Charlson Comorbidity Index [21]. Surgical mortality was defined as death, regardless of its cause, that occurred during the hospital admission in which cardiac surgery was performed. The Cockcroft-Gault equation was used to calculate creatinine clearance [22]. In addition, the Modification of Diet in Renal Disease equation was used to calculate the glomerular filtration rate [23]. Pre-episode renal insufficiency was defined as plasma creatinine over 1.4 mg/dl. New or worsening renal insufficiency during the IE episode was defined as exacerbation of baseline creatinine clearance or plasma creatinine by at least 25% or creatinine levels over 1.4 mg/dl when a previous analysis had been normal. Persistent bacteremia was defined as the presence of positive blood cultures after the first 7 days of treatment. Endocarditis recurrence was defined as a new endocarditis episode during the first years after diagnosis.

4. Patients

Data from patients with IE were analyzed, including clinical manifestations at IE presentation, the pathogens identified, therapy used, morbidity and mortality during hospitalization and during the first year after. A multidisciplinary team evaluated the indication for surgery taking into account, not only immediate surgical risk, but also the chances of long-term survival. Follow-up information was obtained via telephone or through written correspondence with each patient or their primary-care physician. Most patients were treated according to the European endocarditis guidelines [4]. In most cases, the recommended treatment was cloxacillin or vancomycin (if methicillin resistance) together with rifampicin (6 weeks) and gentamicin (2 weeks). The initial dose of vancomycin was 1 g/12 h, and then to maintain minimum blood levels of 15–20 g/ml. Cloxacillin was administered at 2 g/4 h and rifampicin at 300 mg/8 h. Gentamicin was administered at 3 mg/kg/24 h in an attempt to maintain blood concentrations below 1 μg/ml [4,5].

Susceptibility of the causative organism to methicillin determined the choice of therapy. The decision to administer gentamicin corresponded to the attending medical team.

Please cite this article in press as: Ramos-Martínez A, et al., Gentamicin may have no effect on mortality of staphylococcal prosthetic valve endocarditis, J Infect Chemother (2018), https://doi.org/10.1016/j.jiac.2018.03.003