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Original article

Efficacy and safety of outpatient parenteral antibiotic therapy for infective endocarditis: a ten-year prospective study☆

Carlos Cervera[a], Ana del Río[a], Laura García[a], Marta Sala[a], Manel Almela[b], Asunción Moreno[a], Carlos Falces[c], Carlos A. Mestres[d], Francesc Marco[b], Marga Robau[a], José M. Gatell[a], José M. Miró[a,*], the Hospital Clinic Endocarditis Study Group[◊]

[a] *Service of Infectious Diseases, Hospital Clínic-IDIBAPS, University of Barcelona, Barcelona, Spain*
[b] *Service of Microbiology, Hospital Clínic-IDIBAPS, University of Barcelona, Barcelona, Spain*
[c] *Service of Cardiology, Hospital Clínic-IDIBAPS, University of Barcelona, Barcelona, Spain*
[d] *Service of Cardiovascular Surgery, Hospital Clínic-IDIBAPS, University of Barcelona, Barcelona, Spain*

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ABSTRACT

Background: The length of treatment of infective endocarditis (IE) with parenteral antibiotics varies from 2 to 6 weeks. Although several studies indicate that outpatient parenteral antibiotic treatment (OPAT) could be safe for uncomplicated viridans-group streptococci (VGS) IE, the experience in Spain is limited and data on other types of endocarditis and OPAT are scarce worldwide.
Methods: Prospective single center study of a cohort including all patients with IE admitted to the Hospital Clinic of Barcelona OPAT program from January 1997 to December 2006.
Results: During the study period, 392 consecutive episodes of IE in non-drug abusers were attended to. Of these, 73 episodes (42 native-valve, 23 prosthetic-valve, and 8 pacemaker-lead) were admitted to the OPAT program (19%). The percentage of inclusion was higher for viridans group streptococci (VGS) or *Streptococcus bovis (S. bovis)* IE (32% of all VGS or *S. bovis* IE episodes diagnosed *vs.* 14% of the remaining etiologies, *P*<.001). Twelve patients (16%) were readmitted due to complications, of which 3 died (4%). Glycopeptides use was the only predictor factor of hospital readmission (OR 4.5, 95% confidence interval 1.2; 16.8, *P*=.026). No differences in OPAT outcome were found between VGS plus *S. bovis* IE and *Staphylococcus aureus (S. aureus)* plus coagulase-negative staphylococci IE. Patients spent a median of 17 day on OPAT (interquartile range 11-26.5), which enabled 1,466 days of hospital stay to be saved.
Conclusions: These data suggest that OPAT for IE may be a safe and effective therapeutic approach in the treatment of selected patients with types of endocarditis other than uncomplicated VGS or *S. bovis* endocarditis, although patients taking glycopeptides need close clinical OPAT monitoring.

Eficacia y seguridad del tratamiento antibiótico parenteral a domicilio en la endocarditis infecciosa: estudio prospectivo de 10 años

Palabras clave:
Endocarditis infecciosa
Tratamiento antibiótico parenteral a domicilio
Estreptococo grupo viridans
Streptococcus bovis
Staphylococcus aureus
Estafilococo coagulasa negativo

RESUMEN

Antecedentes: La duración del tratamiento antibiótico endovenoso de la endocarditis infecciosa (EI) oscila entre 2 y 6 semanas. Aunque varios estudios indican que el tratamiento antibiótico a domicilio endovenoso (TADE) es seguro para el tratamiento domiciliario de la EI sobre válvula nativa no complicada por estreptococos del grupo viridans (EGV) la experiencia en España con TADE en la EI es limitada y los datos sobre otros tipos de endocarditis y TADE son escasos en todo el mundo.
Métodos: Estudio unicéntrico, prospectivo, de una cohorte de todos los pacientes con EI admitidos en el programa TADE en el Hospital Clínico de Barcelona entre enero de 1997 y diciembre de 2006.

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* Corresponding author.
E-mail address: jmmiro@ub.edu (J.M. Miró).

◊ The list of the members of the Hospital Clinic Endocarditis Study Group is shown in Appendix 1.

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Enterococcus faecalis
Endocarditis de válvula nativa
Endocarditis de válvula protésica
Infección de dispositivo intravascular
Glucopéptidos

Resultados: Durante el período de estudio se diagnosticaron 392 episodios consecutivos de EI en pacientes no consumidores de drogas, de los cuales 73 episodios (19%) fueron admitidos en el programa de TADE: 42 EI sobre válvula nativa, 23 EI sobre válvula protésica y 8 EI sobre cable de marcapasos. El porcentaje de inclusión en la TADE fue mayor para la EI por EGV o *Streptococcus bovis (S. bovis)* (32%) que para el resto de etiologías (14%; p < 0,001). Doce pacientes (16%) fueron reingresados debido a las complicaciones de los cuales tres fallecieron (4%). El uso de glucopéptidos fue el único factor predictor de reingreso hospitalario (OR [intervalo de confianza del 95%] 4,5 [1,2; 16,8] p = 0,026). No se observaron diferencias entre las EI por EGV y *S. bovis* y las EI estafilocócicas (*Staphylococcus aureus* y estafilococos coagulasa-negativos) incluidas en el TADE. Los pacientes incluidos estuvieron una mediana de 17 días en tratamiento domiciliario (rango intercuartílico de 11 a 26,5), lo que permitió un ahorro de 1.466 días de estancia hospitalaria.
Conclusiones: Estos datos sugieren que la TADE en la EI es una estrategia terapéutica segura y eficaz en el tratamiento domiciliario de pacientes seleccionados con EI por EGV y otras etiologías, aunque los pacientes que reciben glucopéptidos precisan un mayor control clínico.

Introduction

Outpatient parenteral antibiotic therapy (OPAT) has been shown to be efficacious, safe, and cost-effective for a wide variety of infectious diseases.[1] The indications for its use in infective endocarditis (IE) are supported by a small number of observational descriptions of short American[2–7] and European[8–10] series, and complete medical data are available only for uncomplicated viridans-group streptococci (VGS) native-valve endocarditis. However, experience with OPAT administered to treat IE in Europe is limited.[8–10]

Antibiotic regimens for IE require 2-6 weeks of parenteral treatment, as oral therapy is not recommended.[11] Thus, OPAT is a highly attractive option for reducing the length of hospital stay and the number of stay-related complications. Before considering outpatient therapy, most patients with IE should be evaluated and stabilized in hospital. Patients selected for home parenteral therapy should have a low risk for congestive heart failure and systemic emboli, which are the most frequent complications of endocarditis. The period of highest risk for systemic emboli is within the first 2 weeks of antimicrobial therapy.[12] The presence of congestive heart failure, neurological findings resulting from systemic emboli, cardiac conduction abnormalities, valve ring abscesses, persistent fever, and positive blood cultures should preclude home intravenous therapy.[11] Prosthetic-valve endocarditis was also excluded from OPAT in the American Heart Association guidelines,[11] as information regarding this issue is lacking. However, data from previous studies suggest that it is safe in selected patients with non-VGS IE.[10,13]

We describe the efficacy and safety —including patient outcome and requirement for readmission— of OPAT in patients with IE admitted to a specialized OPAT program in Spain between 1997 and 2006.

Methods

The Hospital Clinic Infective Endocarditis Study Group has been in existence since 1979. Its characteristics have been described elsewhere.[14,15] All patients with a diagnosis of IE were prospectively evaluated to be admitted to an OPAT program from 1997, when the OPAT unit was created,[16] to December 2006. Patients fulfilling the criteria for OPAT (see below) were included in the program. The 2 main functions of the program were to provide parenteral antimicrobial agents in an outpatient setting and clinical or analytical monitoring to achieve early hospital discharge or to control adverse-effects of antibiotics with a high risk of toxicity.[16] The diagnosis of IE was defined following the modified Duke criteria.[17] The inclusion criteria of patients with IE were adapted from those published by Andrews and von Reyn[18] and are summarized in Table 1. Briefly, patients living near the hospital with adequate family support, absence of intravenous drug use, and stable endocarditis treated in-hospital for at least 7 days, were eligible for inclusion once patient and family consent had been given. Prosthetic-valve IE did not preclude admission to OPAT. The OPAT program was physician-guided. All patients received antimicrobial therapy in their home or long-term care facility.

Antibiotics were administered in 3 ways: *1)* Standard treatment: Daily visits and gravity-based diluted antibiotic bolus administration by a nurse; *2)* Self-administration: Administration by the patient or a family member of the night-dose in the case of twice-daily administered antibiotic or occasional self-administration of ceftriaxone (1 or 2 doses). Only those patients with full autonomy or close support by relatives were allowed to use self-administration of antibiotics; and *3)* Portable infusion-pump system: To administer antibiotics with 2 or more doses/day and adequate stability (24 hours or more) in solution, we used an electronic portable infusion-pump system (CADD-Legacy™ PLUS, Deltec Inc., St. Paul, Minnesota, USA) programmed for intermittent pulses (ampicillin or cloxacillin). Ampicillin was diluted in 500 milliliters of 0.9% sodium chloride, as at this concentration this antibiotic is stable for 24 hours (antibiotic concentrations 24 hours after the ampicillin solution preparation of 90% by HPLC and 76% by bioassay).[19] The dilution of cloxacillin was considered stable for 24 hours following the IDSA guidelines.[1]

Variables were collected prospectively using a specific MS-Access database. Age, gender, underlying chronic diseases, microbiological characteristics, type of endocarditis, antibiotic treatment, days on OPAT, and outcome measures (hospital readmission and mortality) were collected. All patients had at least 1 year

Table 1
Eligibility criteria for inclusion of patients with endocarditis in an OPAT program

Logistic criteria:
- Patient and family consent
- Autonomy or family support
- Residence in the metropolitan area of the hospital
- Telephone contact
- Absence of intravenous drug addiction

Endocarditis criteria:
- Native-valve IE by VGS, *S. bovis*, *S. aureus*, *Enterococcus spp*, coagulase-negative staphylococci or HACEK
- Late prosthetic-valve IE
- Control of infection: negative blood cultures (3 d) and apyrexia (7 d)
- Hemodynamic and electrophysiological stability
- Absence of cardiac abnormalities (severe valve regurgitation, paravalvular abscess by TTE/TEE)
- Absence of extracardiac abnormalities
- At least 7 days of in-hospital treatment

Source: modified from Andrews and von Reyn[18].
HACEK, *Haemophillus* spp., *Actinobacillus* spp., *Cardiobacterium* spp., *Eikenella* spp. and *Kingella* spp.; IE, infective endocarditis; TTE/TEE, transthoracic echocardiography/transesophageal echocardiography; VGS, viridans-group streptococci.