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Outpatient parenteral antimicrobial therapy for infective endocarditis in patients over 80 years

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ABSTRACT

Introduction. The incidence of infective endocarditis is progressively increasing, especially in elderly patients. Outpatient parenteral antibiotic therapy (OPAT) is being an excellent alternative for treatment, but advanced age is one of the relative contraindications. The aim of this study is to compare the characteristics and prognosis of patients less or more than 80 years, treated with OPAT.

Material and methods. One hundred and ninety four patients were included between 1996 and 2015, 31 of them older than 80 years.

Results. The most frequently affected valve is the aortic one, mainly native valves. Most used antibiotics are ceftriaxone, ampicillin, cloxacillin and daptomycin. Differences in surgery (39.9% vs 9.7%, $p=0.001$) and use of infusion pump (55.2% vs 35.5%; $p=0.044$) were observed, under 80 years and older respectively. No differences in readmissions and mortality were observed.

Conclusions. OPAT could be considered an effective alternative for appropriately-selected elderly patients with infective endocarditis.

KEY WORDS: endocarditis, advanced, age, OPAT, antibiotics.

Terapia antibiótica domiciliar endovenosa en pacientes mayores de 80 años con endocarditis infecciosa

RESUMEN

Introducción. La incidencia de la endocarditis infecciosa ha aumentado progresivamente, especialmente en pacientes de edad avanzada. La terapia antibiótica domiciliar endovenosa (TADE) es una excelente alternativa de tratamiento, aunque la edad avanzada sea en algunas guías una contraindicación relativa. El objetivo de este estudio es comparar las características y el pronóstico de pacientes mayores y menores de 80 años tratados con TADE.

Material y métodos. Fueron incluidos 194 pacientes entre los años 1996 y 2015, 31 de ellos con edades superiores a 80 años.

Resultados. La válvula más frecuentemente afectada fue la aórtica, especialmente válvulas nativas. Los antibióticos más utilizados fueron la ceftriaxona, ampicilina, cloxacilina y daptomicina. Se observaron diferencias en cirugía (39,9% vs 9,7%, $p=0,001$) y en uso de bombas de infusión (55,2% vs 35,5%; $p=0,044$), en los grupos menores y mayores de 80 años respectivamente. No se observaron diferencias significativas en reingresos y mortalidad.

Conclusiones. La TADE podría considerarse una alternativa adecuada en pacientes de edad avanzada con endocarditis infecciosa adecuadamente seleccionados.

PALABRAS CLAVE: endocarditis, edad, avanzada, TADE, antibióticos.

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INTRODUCTION

Infective endocarditis (IE) is an infrequent pathology, although there have been progressively increasing incidence in industrialised countries over the past decade^{1,2}. Today, there are between 3-10 cases per 100,000 inhabitants³. In Spain, a recent cohort study with different hospitals estimated 3.5 cases per every 100,000 inhabitants⁴. In this same direction, frequency in the diagnosis of this pathology in elderly patients is increasing and they present higher associated morbidity and mortality^{5,6}.

Over the past years, the most usual treatment for IE is outpatient parenteral antibiotic therapy (OPAT). Despite a lack of bibliography on risk factors that may contraindicate OPAT, advanced age is deemed to be one of them, given that it has been proven that age is an independent mortality risk factor for IE⁷.

Latest guidelines recommend individualised evaluation after the critical phase of 1-2 initial weeks of treatment. Age is not considered a contraindication, although elderly patients more easily have associated comorbidities that do contraindicate or make it difficult to manage OPAT, so this should be taken into account^{8,9}.

The aim of this study is to describe and compare characteristics of patients diagnosed with IE in our centre and discharged with OPAT, comparing the group of elderly patients and those under 80 years of age, and the differences between them.

MATERIAL AND METHODS

All patients diagnosed with IE at Hospital Donostia between the years 1996 and June 2015 were included prospectively, treated with OPAT at our Outpatient Hospitalisation Service (OHS). In total, 194 patients were included. Patients were defined by Duke criteria (until the year 2000) and modified Duke criteria (2000-2015) as possible or definitive¹⁰.

All of the cases were divided into two sub-groups: those under 80 years when diagnosed, and those 80 or older. Demographic (age, sex), diagnostic (diagnostic by Duke criteria, aetiology, valve type, affected valve), treatment (surgery, used antibiotics, treatment duration) and result variables (complications, readmission and mortality) were obtained. These variables were compared in both sub-groups to discover the differences between them.

Qualitative variables were presented in proportions and compared by using the χ^2 test. To compare quantitative variables in both sub-groups, the t-student test was used. For all calculations, statistical significance was determined with a reliability interval of 95%. This analysis was made with the statistical package SPSS version 21.0 (IBM, Chicago, IL, U.S.A.).

RESULTS

A total of 194 cases of IE were included. Out of them, 163 were patients under 80 years, and 31 were older. The average

Table 1	Basal characteristics.		
	< 80 years	≥ 80 years	p
Population	163	31	
Sex			0.549
Male	119 (73%)	21 (68%)	
Female	44 (27%)	10 (32%)	
Average age (years)	61	84	
Diagnostic: (Duke)			0.128
Possible	46 (27.2%)	13 (41.9%)	
Definitive	117 (71.8%)	18 (58.1%)	
Aetiology			0.376
<i>S. aureus</i>	19 (11.7%)	2 (6.5%)	
<i>Enterococcus</i>	25 (15.3%)	3 (9.7%)	
Coagulase negative	29 (17.8%)	3 (9.7%)	
Viridans group streptococci	57 (35.0%)	16 (51.6%)	
Other	25 (15.3%)	4 (12.9%)	
Negative cultures	8 (4.9%)	3 (9.7%)	
Valve type			0.413
Native	81 (49.7%)	15 (48.4%)	
Prosthetic	54 (33.1%)	7 (22.6%)	
Electrocatheter	15 (9.2%)	5 (16.1%)	
Unknown	13 (8.0%)	4 (12.9%)	
Affected valve			0.159
Aortic	69 (42.3%)	13 (41.9%)	
Mitral	50 (30.7%)	6 (19.4%)	
Right	5 (3.1%)	3 (9.7%)	
Multi-valvular	11 (6.7%)	0 (0%)	
Electrocatheter	15 (9.8%)	5 (16.1%)	
Unknown	13 (8.0%)	4 (12.9%)	

patient age was 65 years (range: 25-92). Table 1 shows demographic characteristics and diagnostics of both groups.

The definitive diagnostic according to Duke Criteria is greater in the sub-group with those under 80 years (71.8 vs 58.1%; $p = 0.128$). The predominant microorganism are viridans group streptococci in both sub-groups, although an increase in prevalence was observed in the sub-group of those over 80 (51.6% vs 35%). The most frequently affected valve is the aortic valve for both groups, with similar rates for those both under and over 80 years of age, respectively (49.7% vs 48.4%). These were mainly native valves, with 49.7% in those under 80 years of age vs 48.4% in those older, with a slight increase in electrocatheter affection for the latter sub-group (16.1% vs 9.2%) in comparison with prosthetic valve affection (22.6% vs 33.1%). In the prosthetic valve group, 2 patients

Table 2 Treatment and prognosis characteristics.

	< 80 years	≥ 80 years	p
Population	163	31	
Surgery	65 (39.9%)	3 (9.7%)	0.001
Use of infusion pumps	90 (55.2%)	11 (35.5%)	0.044
Infusion method complications	23 (14.8%)	3 (9.7%)	0.507
Total treatment duration (days)*	39 (±15.7)	35 (±12.9)	0.182
Hospital treatment duration (days)*	17 (±10.5)	11 (±6.4)	0.003
Outpatient treatment duration (days)*	22 (±14.5)	24 (±13.6)	0.375
Readmissions	27 (16.6%)	8 (25.8%)	0.22
Mortality	1 (0.61%)	0 (0%)	0.66

*Mean and standard deviation

were included with transcatheter aortic valve implantation (TAVI), one in each sub-group.

The antibiotic used for treatment with those under and over 80 years was, respectively: vancomycin (4.9% vs 3.2%), daptomycin (12.9% vs 12.9%), cloxacillin (14.7% vs 6.5%), ampicillin (24.5% vs 22.6%), ceftriaxone (31.9% vs 48.4%) and other antibiotics (11% vs 6.5%). Variables in treatment and results are shown on table 2. The percentage of patients that finished oral antibiotic treatment was 18.4% vs 16.1%, respectively. Surgical treatment was conducted more frequently on those under 80 years (39.9% vs 9.7%; $p=0.001$). Complications in infusion were similar (14.8% for those under vs 9.7% for those over 80), the most frequent being: phlebitis (69.2%), antibiotic extravasation (7.7%), thrombosis (7.7%) and other causes (15.4%).

Readmissions were more frequent with the sub-group over 80 years, although with a non-significant difference (8 cases: 25.8% vs 27 cases: 16.6%; $p=0.22$). The causes for re-admission were: fever (31.5%), catheter complications (11.4%), embolic phenomena (11.4%), cardiac failure (11.4%), kidney failure (11.4%), scheduled surgery (8.6%) and other causes (14.3%). Only one patient was deceased, belonging to the sub-group under 80 years.

DISCUSSION

Cases of IE in elderly patients are increasing in our environment. In addition to greater life expectancy, causes may include greater prevalence of predispositional cardiopathy, higher use of electrocatheters and a greater number of urinary and gastrointestinal infections giving way to bacteraemia¹¹.

Over the past decades, an increase in IE has been observed, caused by *Staphylococcus aureus* and enterococci, associated with a decrease in those caused by *Streptococcus*⁶. Notwithstanding, with elderly patients there is great controversy in regards to the high percentage of IE caused by viridans group

streptococci. In our cohort, the prevalence of IE caused by viridans group streptococci was greater in the sub-group of those older than 80 years than observed in other studies¹². On the other hand, there are studies where this increase in prevalence is not observed with this patient sub-group¹³.

There is a great difference between patients treated surgically with the two sub-groups in our study, being strikingly lower in the elderly. Several works have been published that reached the same conclusion^{12,13}. This may be due to fewer associated valvular complications in elderly patients, a greater number of comorbidities making surgery difficult, and the more favourable microbiological profile in the work published by López et al, where 600 patients were prospectively analysed in 3 tertiary centres.

The duration of the hospital stay was much greater for patients under 80 years of age. This is most likely due to higher surgery rates in this group, so the patient is released later. In a prospective Spanish cohort with 582 patients, López-Wolf et al obtained the same result¹².

OPAT has proven itself to be a highly effective tool in treating IE. IE treatment guidelines do not contraindicate this procedure for age. They recommend an initial 2-week phase until the patient is stabilised before evaluating OPAT according to clinical stability^{7,8}. Few cohorts have studied failure risk factors for this type of therapy. A study conducted in Great Britain, which included 80 IE episodes, defined the risk factors related to OPAT failure. Failure was defined as readmission or unscheduled surgery, adverse effects to the medication obliging readmission, or changes in the pattern and development of resistance to the antibiotic treatment used. In the multivariate analysis, only heart failure, kidney failure and treatment with teicoplanin proved to be risk factors associated with OPAT failure. Regarding to the age, even those patients that failed were older than those who did not (67.1 vs 59.1; $p=0.466$), the difference was not statistically significant¹⁵. The frequent use of infusion pumps (52% of total patients) is not very common in the literature¹⁶, but it facilitates the use of different antibiotics, even for the group of those over 80 years, who have a high rate of treatment with these devices, despite being significantly less frequent than in the other sub-group (55.2% vs 35.5%).

In our study, the global readmission rate is 18%, and the mortality rate is 0.51%. In the scientific literature, there are few studies to compare said rates. In the prospective study conducted in New Zealand by Amodeo et al¹⁷, rates, respectively, were 10% and 0% for a cohort of 100 patients diagnosed with IE and treated with OPAT. In this case, the average patient age was similar (64.5 years) and 18% were not treated at their homes, but rather at residential facilities. Not counted as readmissions were patients that needed a scheduled valve replacement, as considered in our case. In another study conducted in Barcelona by Cervera et al¹⁸, 73 patients were treated with OPAT, with a lower average age (59.5 years) and readmission and mortality rates at 16% and 4%, respectively.

Another one of the advantages OPAT provides in treating patients diagnosed with IE is the secondary economic savings.

Lacroix et al published a work that estimated savings brought about by this type of therapy¹⁹. This was a retrospective observational study that compared 39 IE diagnoses, 18 of them treated as outpatients and 21 completing the entire antibiotic cycle at the hospital. It was estimated that savings brought about by this treatment were approximately 15,000 euros for each patient treated as an outpatient. In our case, it was not possible to obtain this data, although the similarity of the health system suggests that savings could be similar.

The limitations in our work are mainly the low number of patients older than 80 years treated with OPAT for an IE episode. In the bibliography analysed, no series were found with a greater number of elderly patients, although progressively, as mentioned beforehand, there will be an increase in this profile type in our environment over the years to come. Another limitation is the heterogeneity that may exist in cohorts that span so many years, such as ours. Patients were included over a period of almost 20 years, which makes it difficult to analyse results, given the changes taking place during this period in diagnosis, treatment and monitoring. Lastly, another widely-debated issue is the arbitrariness in selecting age limits. In the scientific literature, there is a trend for the age considered to be elderly to go up over the past years. Studies are observed with different limits between 65 and 80 years, which means results obtained must be compared with caution.

In conclusion, no differences were observed in complication, readmission or mortality rates between the two subgroups of those older and younger than 80 years of age. The frequent use of infusion pumps in our environment, including for elderly patients, facilitates OPAT, with a greater therapeutic arsenal. As such, OPAT may be considered an effective alternative for appropriately-selected elderly patients diagnosed with IE, which would furthermore bring about great economic savings for the health system.

REFERENCES

- Pant S, Patel NJ, Deshmukh A, Golwala H, Patel N, Badheka A et al. Trends in infective endocarditis incidence, microbiology, and valve replacement in the United States from 2000 to 2011. *J Am Coll Cardiol* 2015 ;65:2070-6
- Fedeli U, Schievano E, Buonfrate D, Pellizzer G, Spolaore P. Increasing incidence and mortality of infective endocarditis: a population-based study through a record-linkage system. *BMC Infect Dis* 2011 ;11:48.
- Cahill TJ, Prendergast BD. Infective endocarditis. *Lancet*. 2016 ;387:882-93
- Muñoz P, Kestler M, De Alarcon A, Miro JM, Bermejo J, Rodríguez-Abella H et al. . Current Epidemiology and Outcome of Infective Endocarditis: A Multicenter, Prospective, Cohort Study. *Medicine (Baltimore)*. 2015 ;94:e1816.
- Leone S, Ravasio V, Durante-Mangoni E, Crapis M, Carosi G, Scotton PG et al. Epidemiology, characteristics, and outcome of infective endocarditis in Italy: the Italian Study on Endocarditis. *Infection*. 2012 ;40:527-35.
- Slipczuk L, Codolosa JN, Davila CD, Romero-Corral A, Yun J, Pressman GS. et al. Infective endocarditis epidemiology over five decades: a systematic review. *PLoS One*. 2013 ;8:e82665.
- Durante-Mangoni E, Bradley S, Selton-Suty C, Tripodi MF, Barsic B, Bouza E et al. Current features of infective endocarditis in elderly patients: results of the International Collaboration on Endocarditis Prospective Cohort Study. *Arch Intern Med*. 2008 168:2095-103.
- Baddour LM, Wilson WR, Bayer AS, Fowler VG Jr, Tleyjeh IM, Rybak MJ et al. Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications: A Scientific Statement for Healthcare Professionals From the American Heart Association. *Circulation*. 2015 ;132:1435-86.
- Habib G, Lancellotti P, Antunes MJ, Bongiorno MG, Casalta JP, Del Zotti F et al. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC) Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). *Eur Heart J*. 2015 ; 36:3075-128.
- Li JS, Sexton DJ, Mick N, Nettles R, Fowler VG Jr, Ryan T et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis*. 2000; 30:633-8.
- Fernández-Hidalgo N, Tornos Mas P. Epidemiology of infective endocarditis in Spain in the last 20 years. *Rev Esp Cardiol (Engl Ed)*. 2013; 66:728-33.
- López-Wolf D, Vilacosta I, San Román JA, Fernández C, Sarriá C, López J et al. . Infective endocarditis in octogenarian patients. *Rev Esp Cardiol*. 2011; 64:329-33.
- Remadi JP, Nadji G, Goissen T, Zomvuama NA, Sorel C, Tribouilloy C. Infective endocarditis in elderly patients: clinical characteristics and outcome. *Eur J Cardiothorac Surg*. 2009; 35:123-9.
- López J, Revilla A, Vilacosta I, Sevilla T, Villacorta E, Sarriá C et al. Age-dependent profile of left-sided infective endocarditis: a 3-center experience. *Circulation*. 2010; 121:892-7.
- Duncan CJ, Barr DA, Ho A, Sharp E, Semple L, Seaton RA. Risk factors for failure of outpatient parenteral antibiotic therapy (OPAT) in infective endocarditis. *J Antimicrob Chemother*. 2013;68:1650-4.
- Candel FJ, Julián-Jiménez A, González-Del Castillo J. Current status in outpatient parenteral antimicrobial therapy: a practical view. *Rev Esp Quimioter*. 2016; 29:55-68.
- Amodeo MR, Clulow T, Lainchbury J, Murdoch DR, Gallagher K, Dyer A et al. Outpatient intravenous treatment for infective endocarditis: safety, effectiveness and one-year outcomes. *J Infect*. 2009; 59:387-93.
- Cervera C, del Río A, García L, Sala M, Almela M, Moreno A et al. Efficacy and safety of outpatient parenteral antibiotic therapy for infective endocarditis: a ten-year prospective study. *Enferm Infecc Microbiol Clin*. 2011; 29:587-92.
- Lacroix A, Revest M, Patrat-Delon S, Lemaître F, Donal E, Lorréac'h A et al. Outpatient parenteral antimicrobial therapy for infective endocarditis: a cost-effective strategy. *Med Mal Infect*. 2014;44:327-30.