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Determinants and Results of Early Surgery for Prosthetic Valve Endocarditis with Periannular Extension

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Abstract: Infective endocarditis (IE) is a rare but potentially fatal complication of valve replacement, especially if it is accompanied by periannular extension. In these cases surgical intervention is recommended by consensus and clinical guidelines. However, surgery is frequently delayed or not performed, and the best timing for intervention is still controversial. The aim of this study is to analyze determinants of early surgery of patients with prosthetic valve endocarditis (PVE) with periannular extension (PVEPE) and the influence of timing for surgery in morbidity and mortality in a real clinical scenario. Retrospective analysis of a prospective database registry including 180 consecutive patients with definite diagnosis of endocarditis according to modified Duke`s criteria, admitted between 6/2008 and 1/2016, showed 88 patients (49%) with PVE, 48 (54.5%) of them had periannular extension. The patients with PVEPE were divided in 3 groups according to timing for surgery after admission: GA (17p; <10 days), GB (15p; >10 days) and GC (16p; only medical treatment). We analyzed demographic, clinical, microbiological and echocardiographic variables and we related the treatment strategy selected with in-hospital evolution. Comparing the 3 different groups, we observed that the patients in GA were significantly younger, with a higher frequency of male gender and *Staphylococcus spp* was significantly the most common microorganism; they had less postoperative complications (64% vs 100%, p: 0.019) and a trend to lower in-hospital mortality (18% vs 46%; p= 0,07). In conclusion, younger male patients with staphylococci PVEPE underwent surgery earlier. This strategy was associated with less anatomical damage and less incidence of postoperative complications with a trend to lower in-hospital mortality.

Keywords: Prosthetic Valve Endocarditis, Endocarditis, Periannular Extension, Early Surgery, Echocardiography

1. Introduction

Prosthetic valve endocarditis (PVE) is a rare but potentially fatal complication of valve replacement, with an incidence of approximately 1% to 2% per patient-year. [1] Periannular extension of infection is one of the most fearful complications and it is well recognized that this particular condition casts a shadow over the prognosis of patients with PVE. Despite the growing experience in diagnosis and treatment of specialized centers, in-hospital mortality of patients with PVE remains high (20-40%), and may be even greater in cases with periannular extension. [2-6]

Several observational studies, most of them retrospective, have explored the impact of early surgery in the management of active endocarditis, with no consistent results. [7-13] At the present time, there is only one randomized controlled trial

that attempted to assess the optimal time for surgical intervention in native valve endocarditis. Although very valuable in design, its results could not be extrapolated to other scenarios for different reasons: sample size, most common microorganism and inclusion criteria, among others. [13]

Infective endocarditis is a condition that may require a medical and surgical approach. Cases affecting intracardiac devices such as prosthetic valves often require the surgeon's intervention. However, the effect of surgical therapy on outcome of PVE is controversial and poorly understood due to, in part, prospective randomized trials are still lacking. Although some authors claim that medical treatment can be sufficient for some patients, most series suggest that in patients with PVE early surgery is associated with better results, particularly in patients complicated with periannular extension. [1, 13-17] International guidelines [1, 3] provide strong recommendations to manage PVE, although these recommendations are not based on strong clinical evidence, but primarily on expert opinions and case series.

Also, the timing to intervention is under review and, in the clinical practice, surgery is frequently delayed for reasons not fully elucidated yet. Finally, it is not clearly established what is ment by "early surgery" and the time considered by different groups of experts is highly variable (2, 3, 5, 7, 10 days). [18-21] The aim of this study is to assess determinants of early surgery of patients with PVEPE in a real clinical scenario and the influence of timing for surgery in morbidity and mortality in a third level, monovalent, cardiovascular center.

2. Methods

This is a retrospective analysis of a prospective database registry that includes patients with definite diagnosis of infective endocarditis who were consecutively admitted at the Instituto Cardiovascular de Buenos Aires between June 2008 and January 2016. Definite endocarditis was confirmed according to the modified Duke criteria. [22, 23] Etiologic microorganisms were considered those that were isolated either from peripheral blood cultures, valvar tissue sample and/or extra or intracardiac thrombus obtained during the surgical procedure. At admission, all patients underwent both modalities of echocardiographic imaging, transthoracic (TTE) and transesophageal (TEE), with a mean delay of 1,5 days (range: 0-4 days). Images were interpreted by experienced cardiologists with the assessments of valve function, vegetations, presence of periannular complications and left ventricular performance.

Perivalvular extension was define as the presence of 1-Abscess, 2-Pseudoaneurysm, 3-Fistula or 4-periprosthetic leak. A perivalvular abscess was defined as a closed cavity of heterogeneous acoustic density without flow inside; pseudo-aneurysm as a pulsatile cavity of reduced echo density communicating with the cardiovascular lumen with color flow detected in its interior, a fistula was defined as a communication between two neighboring heart cavities through a color Doppler tract and, finally, the finding of a periprosthetic leak was considered significant when the regurgitation generated by it was of a moderate to severe magnitude, valued though the usual qualitative and quantitative echocardiographic parameters. [24]

Given the lack of a universal definition "early" surgery was arbitrarily considered when the procedure was performed within the first ten days after hospital admission and "late" after that period.

Patients with PVEPE were selected and divided into three groups according to the therapeutic strategy selected and the time to surgical intervention from the time of admission: GROUP A (GA): patients who received medical treatment and early surgery; GROUP B (GB): patients that received medical treatment and late surgery; and GROUP C: patients under medical therapy alone.

Taking into consideration the guidelines in force at the time of decision making in each patient, the decisions about surgical treatment were taken according to the medical judgment of the attending physician and the opinion of the local Endocarditis team (constituted by cardiologist, cardiovascular surgeons, echocardiographers, infectious diseases specialists and microbiologists) and were individualized to each patient in their own particular clinical scenario. [2, 3]

Serious events occurring after valve replacement surgery were considered postoperative complications, such as: prolonged mechanical ventilation (>48-72 hs), cardiogenic shock, mediastinitis, septic shock, complete atrioventricular block with pacemaker requirement and renal failure with dialysis requirement.

In the statistical analysis discrete variables were expressed as an absolute value (percentage) and continuous data as mean (+/- standard deviation) in case of normal distribution and, otherwise, as median (interquartile range). The chi2 test was used to compare the qualitative variables and Fisher´s exact test was used when necessary. Continuous variables were compared using the Student *t* test or its nonparametric equivalent, the Mann-Witney *U* test. Due to the low number of patients, a univariate analysis was performed to determine the determinants of early surgery. A p value less than 0.05 was used as the cutoff for statistical significance.

3. Results

During the study period 180 patients with definite diagnosis of infective endocarditis were consecutively admitted: 88 patients (49%) had PVE and 48 of them (54.5%) had periannular extension. These 48 patients with PVEPE represent our study population and were divided in three groups according to the therapeutic strategy selected. Each group was represented as follows: GA (early surgery): 17 patients (35.4%), GB (late surgery): 15 patients (31.2%) and GC (no urgery): 16 patients (33.3%).

Table 1 shows demographic and clinical findings of the study population. The mean age was 67 +/- 11 years and 63% were males. Of note, the patients in GB and GC were

significantly older than patients in GA and a significant higher frequency of male gender was observed in GA in comparison with GB and GC.

There were 17 patients (34%) with early PVE (<12 months after valve replacement surgery) with a non-significant trend to a higher frequency of this diagnosis in GA.

Remarkable is the fact that all patients presented with fever and only 5 patients (10%) had heart failure at admission, with no significant differences between the three groups.

Table 1. *Demographic, epidemiological and clinical characteristics at admission.*

	GROUP A (n = 17)	**GROUP B (n = 15)**	**GROUP C (n = 16)**	**P value**
Demographic and epidemiological variables:				
Age (years) Median (IQR)	66 (55,5-69,5)	68 (64-72)	79 (70,2-83)	0.004
Men N (%)	15 (88,2)	6 (40)	9 (56,2)	0.012
Hypertension N (%)	12 (70,6)	10 (66,6)	12 (75)	0.924
Diabetes N (%)	4 (23,5)	3 (20)	4 (25)	0.943
Chronic Renal Failure N (%)	1 (5,9)	0	3 (18,7)	0.198
Coronary Artery Disease N (%)	1 (5,9)	4 (26,6)	6 (37,5)	0.08
Intracardiac Devices N (%)	2 (11,8)	5 (33,3)	1 (6,2)	0.136
Previous Endocarditis N (%)	3 (17,6)	3 (20)	4 (25)	0.907
Early prosthetic valve endocarditis N (%)	8 (47%)	5 (33,3)	4 (25)	0.419
Clinical characteristics at admission:				
Fever N (%)	17 (100)	15 (100)	16 (100)	-
Heart Failure N (%)	1 (5,9)	2 (13,3)	2 (12,5)	0.724
Septic Shock N (%)	2 (11,8)	1 (6,6)	1 (6,2)	1
Embolics events N (%)	5 (29,4)	4 (26,6)	4 (25)	1
Complete Atrio-ventricular Block N (%)	0	1 (6,6)	2 (12,5)	0.402
Surgical Risk:				
Logistic Euro Score Mean (ED)	24,8 (9,3)	31,7 (16,2)	43,7 (13)	0.001

The causative microorganism could be identified in 85% of the patients (Table 2). A significant higher frequency of staphylococcal infection was observed in GA and enterococci leads as most prevalent causative pathogen in groups B and C.

Table 2 shows the echocardiographic findings before the surgical procedure or at the end of the patient follow-up. Aortic prosthetic valves were the ones most frequently affected, reaching 89% of cases when biological and mechanical prostheses were considered. No significant differences between groups were observed in regards to the left ventricular systolic function parameters, considering the left ventricular ejection fraction and end-systolic diameter.

Comparative analysis between the groups shows that GA in comparison with GB had a significant higher frequency of abscess (65% vs 26%, p: 0.016) and lower frequency of periprosthetic leak (12% vs 53%, p: 0.011). When the findings of leak, fistula and pseudo-aneurysm were combined to obtain a single variable, in an attempt to group those findings related to greater local conminent, a statistically significant difference in its frequency was observed in GA in comparison with GB and GC (29% vs 80% vs 69%, p: 0.009), with less frequency in GA where the most prevalent finding was abscess.

Table 2. *Microbiological profile and Echocardiographic data.*

	GROUP A (n = 17)	**GROUP B (n = 15)**	**GROUP C (n = 16)**	**P value**
Microbiological profile N (%)				
Positive blood cultures	15 (88,2)	11 (73,3)	15 (93,7)	0.263
Streptococcus sp	3 (17,6)	3 (20)	3 (18,7)	1
Staphylococcus sp	11 (64,7)	2 (13,3)	4 (25)	0.007
Staphylococcus Aureus	7 (41,2)	2 (13,3)	2 (12,5)	0.110
Coagulase Negative Staphylococcus	5 (29,4)	0	2 (12,5)	0.055
Enterococcus	0	5 (33,3)	6 (37,5)	0.009
HACEK	1 (5,8)	0	2 (12,5)	0.638
Echocardiographyc data:				
Affected valve: N (%)				
Biological Aortic Prostheses	12 (70,6)	8 (53,3)	8 (50)	
Mechanical Aortic Prostheses	5 (29,4)	6 (40)	4 (25)	
Biological Mitral Prostheses	1 (5,8)	2 (13,3)	1 (6,2)	
Mechanical Mitral Prostheses	1 (5,8)	3 (20)	5 (31,2)	
TAVI	0	0	0	
Left Ventricular Systolic Function:				
LVEF Mean (ED)	58,8 (9,7)	54,8 (10,5)	59,3 (7,2)	0.339
LVDD Mean (ED)	50,4 (6,2)	50 (6,6)	48,6 (6,5)	0.694
LVSD Mean (ED)	26,6 (7,7)	29,4 (7,9)	27,4 (4,5)	0.518
Endocarditis related findings: N (%)				

	GROUP A (n = 17)	GROUP B (n = 15)	GROUP C (n = 16)	P value
Vegetations	6 (35,3)	7 (46,6)	6 (37,5)	0.789
Abscess	12 (70,6)	4 (26,6)	8 (50)	0.046
Pseudo-aneurysm	4 (23,5)	7 (46,6)	6 (37,5)	0.385
Fistula	0	3 (20)	2 (12,5)	0.142
Leak	2 (11,8)	8 (53,3)	7 (43,7)	0.034
Pseudo-aneurysm + Fistula + Leak	5 (29,4)	12 (80)	11 (68,7)	0.009

TAVI: Transarterial Valve Implantation, LVEF: Left Ventricular Eyection Fraction, LVDD: Left Ventricular diastolic diameter, LVSD: Left Ventricular Systolic Diameter.

In order to evaluate surgical risk, logistic EuroSCORE was used. The median score of the entire cohort was 33 (22-73). No statistically significant difference was observed in the surgical risk between GA and GB, but when these groups were compared with GC, higher logistic EuroSCORE was observed in this last group with a significant difference (p: 0.009).

In the course of the disease 32 patients (65%) underwent surgery: 28 during the acute phase and 4 during a new hospital admission for emergency surgery due to progression of the periannular complications, all of them being still under antibiotic treatment. The median time to surgery was 11 days (range = 7-21) in the total population; in GA was 7 days (range = 5-9) and in GB 23 days (range = 13-70; p<0.01).

In a comparative analysis between the groups (Table 3) a higher probability of postoperative complications was observed in GB compared to GA (100% vs 64%, p: 0.019).

There were no differences in the hospitalizations days among the groups. The median time was 21 days (14-47) in GA, 22 (18-43) in GB and 14.5 days (10-40) in GC (p: 0, 19).

Overall, in-hospital mortality was 29.8% (15pts); GA: 3ptes, GB: 7 ptes and GC: 5pts. In the population undergoing surgery (GA and GB) mortality was 20% (10 p). There was a nonsignificant trend to lower in-hospital mortality in GA in comparison to GB (18 vs 46%, p: 0, 07), but when all groups were compared, no significant differences in mortality were observed.

Table 3. *In-Hospital Evolution.*

	GROUP A (n=17)	GROUP B (n=15)	GROUP C (n=16)	P value
Days of hospitalization Median (IQR)	21 (14-47,5)	22 (18-43)	14,5 (10-40,5)	0.192
Postoperative Complications N (%)	11 (64,7)	15 (100)	-	**0.019**
Mortality N (%)	3 (17,6)	7 (46,6)	5 (31,2)	0.21

The univariate analysis (Table 4) between the patients who underwent surgical treatment (GA and GB) shows that the variables related with early intervention were male gender and staphylococcus infection.

In the medium-term follow-up (18 months) no patient from GA presented a new early or late PVE and only 1 patient in group B required hospitalization for relapse of infectious endocarditis.

Table 4. *Univariate analysis for early surgery determinants.*

	GROUP A	GROUP B	OR (CI)	P
Age<70 N (%)	12 (75)	9 (60)	2.33 (0.5-10)	0.14
Male gender N (%)	14 (87.,5)	7 (47)	10 (2-54)	0.004
Absence of coronary artery disease N (%)	15 (94)	11 (73)	6.82 (0.6-59)	0.161
Heart Failure N (%)	1 (6)	2 (13)	0.47 (0.04-6)	0.5
Septic Shock N (%)	2 (12.5)	1 (6.6)	2 (0.2-26)	0.5
EuroScore<30 N (%)	11 (69)	8 (53)	0.48 (0.11-2.04)	0.3
Stafilococcus spp N (%)	11 (64,7)	2 (13,3)	11 (2-50)	0.03

4. Discussion

According to contemporary cases series and population-based studies, it is estimated that PVE accounts for 10-30% of all cases of infective endocarditis and occurs in 1-5% of patients with valve prostheses. This serious complication of valve surgery is associated with high morbidity and mortality (20-40%) especially if it is associated with heart failure and/or periannular extension. [1, 19]

Surgical intervention with debridement of infected tissue and valve replacement is currently recommended by consensus guidelines. [1, 2] However, these guidelines are not based on strong clinical evidence and, in the clinical practice, the final decision of surgery seems to be taken arbitrarily considering general aspects of patients that go beyond the usual considerations. Similarly, the optimal time for intervention is controversial and still under review. [1, 28, 29]

There are no randomized controlled trials attempting to clarify the best treatment option for these patients and literature virtually lacks trials that study the effectiveness of early surgery in the setting of PVEPE.

Almost two thirds of the patients of our study group population underwent surgery, most of them in the index hospitalization. The main determinants of early intervention were male gender and the presence of the fearful

staphylococcal infection, regardless of the mere presence of perivalvular extension or heart failure that are themselves classic indications of surgery. [6, 23]

Surgical procedures required in the context of PVE are technically demanding and associated with a high frequency of postoperative complications and mortality. Surgical mortality ranges from 6 to 25% according to different series [26-30]; these results are consistent with those found in our study population considering the mortality of all patients undergoing surgery, but if those operated after 10 days after admission are considered the mortality observed is higher than the range reported in the literature.

Although we cannot show significant difference in mortality, there was a significant lower incidence of postsurgical complications in patients with early surgery. The results of this study are consistent with recent publications that show that surgery is the best option in PVE, particularly if complicated with perivalvular extension, moreover, that the time to intervention should not be delayed. [6, 15, 26]

Most surgeons would agree that surgical complications and mortality relates to the amount of anatomical damage and it is well known that anatomical destruction relates both to the aggressiveness of the involved microorganism and the duration of the infectious process. It might be supposed that the prognosis would be improved if the surgery takes place early, before the destruction of heart tissue and deterioration of general patient condition occurs. Isolation of virulent pathogens, such as staphylococcus species, was a determining factor in the decision to perform an early intervention in the population analyzed in our study. However, the strategy to reduce the time of evolution of the disease seems not to have been considered in all patients. In the groups where surgery was delayed or not performed, the anatomical damage was more widespread and this was probably reflected in worse clinical outcomes.

In clinical practice, the benefit of operating early and the risks of the surgery itself, should be balanced against a theoretically risk of prosthetic infection and periannular complications. At least in part, this risk depends more on the surgeon`s experience and skills to extirpate all infective tissues than on the time between the beginning of antibiotic therapy and the surgery. In the population analyzed, only one patient in GA was complicated with early PVE and, at the same time, 4 patients in group B, in which an initial conservative management was attempted, required re-hospitalization for emergency surgery due to progression of perivalvular disease.

Limitations: This study has the limitation of being retrospective and, therefore, subject to the occurrence of possible biases. In each patient, the decision to operate or not and the time for surgical intervention were based on the clinical judgment of the medical team and the distribution of the groups in this trial is based precisely on this therapeutic strategy. Also, the population of the study is small and, therefore, a multivariate analysis to determine the independent predictors of early surgery could not be performed.

Prospective studies including more patients would be required to clarify the true effect of surgery in patients with PVEPE and what is the optimal time for surgery and, besides this, which are the real determinants that, in the clinical practice, influence the final therapeutic decision. While awaiting results, the decision for surgery should be made after careful individualized multidisciplinary evaluation.

5. Conclusions

Among patients with PVEPE early surgery showed better clinical outcomes in terms of less severe postoperative complications and a trend to lower in –hospital mortality. These results could be related to less intensive anatomical damage and, consecutively, less technical difficulties of the surgical procedures required in this group of patients.

Glossary of Abbreviations

IE: Infective endocarditis

PE: perivannular extension

PVE: Prosthectic Valve Endocarditis

PVEPE: Prosthetic Valve Endocarditis with Perivalvular Extension

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