Utility of A Cardiorenal Monographic Consultation to Reduce The Cardiovascular Mortality of The Renal Transplant Patient

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Keywords
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Renal transplantation
Coronary revascularization

Abstract

Introduction and objectives: WHO recognizes chronic kidney disease as a serious health problem with increasing incidence and prevalence. In our midst, the first cause of death in renal replacement therapy is cardiovascular disease (CVD), especially ischemic. We studied and follow-up of candidates for renal transplantation and subsequently transplanted, With the objective of knowing the ischemic load and reducing the mortality of the transplant.

Methods: In November 2005, we began a cardiorenal monographic consultation for the study of all patients with chronic renal disease with a high cardiovascular risk who were candidates for renal transplantation and subsequently transplanted, according to the protocol prior to transplantation, were studied.

Results: From November 2005 to December 2013, 313 patients were studied, 64% males, 56.7 ± 11 years old. The Prevalence of significant coronary lesions: 39.3%, 54.4, % of more than one vessel. Silent: 32.4%, 47.6% more than one glass. Total mortality of candidates: 10.2%. Cardiovascular: 4.8%.

Total transplant mortality: 5.3%, cardiovascular: 2.1%. Cardiovascular mortality of the revascularized transplant patient: 0%.

Conclusions: Screening and intervention on CVD, leven preventive, reduce total and cardiovascular mortality of the transplant, extending this benefit to those remaining on dialysis. In our hospital, CVD is no longer the leading cause of death in renal replacement therapy.

Introduction

Chronic kidney disease (CKD) is recognized by the World Health Organization (WHO) as a serious health problem, with a prevalence of approximately 10% according to various epidemiological studies1-5. This prevalence is expected to increase in the coming years6. Many cases remain undiagnosed due to the absence of symptoms; these cases constitute occult renal disease, and as the disease becomes chronic, the prognosis worsens7,8.

CKD is closely associated with several pathologies that are increasingly prevalent and have reached epidemic levels in developed countries, including high blood pressure (HBP), obesity, diabetes mellitus or even aging9. This association increases the cardiovascular risk of these patients, which promotes the development of cardiovascular diseases and further worsens the prognosis. Advanced stage of CKD are directly associated with a greater burden of arteriosclerosis, including coronary artery disease, to the point that more than 50% patients undergoing...
kidney replacement therapy die due to cardiovascular complications. Cardiovascular mortality is the main cause of death in patients undergoing any type of kidney replacement therapy, as well as the first cause of loss of a functioning allograft in transplant patients\textsuperscript{10,11}. In an attempt to reduce cardiovascular mortality, several groups have carried out screening studies of ischemic heart disease in patients undergoing kidney replacement therapy or prior to kidney transplantation\textsuperscript{12,13}, with beneficial effects and promising results.

Hoping to increase survival, the American Transplant Society\textsuperscript{14} and the Integrated Care Process of Kidney Replacement Therapy of the Andalusian Community have recommended that candidates for kidney transplantation who are at high cardiovascular risk, including asymptomatic patients, should undergo screening for myocardial ischemia.

Since 2005, our center has provided cardiology consultation services in order to detect cardiovascular pathology in patients who are candidates for kidney transplantation. For more than 13 years, the purpose of such consultations has been to decrease cardiovascular mortality in transplant patients, which is the leading cause of loss of a functioning allograft.

**Materials and Methods**

**Protocol and patients**

In November 2005, a protocol was established between the Department of Nephrology and Department of Cardiology of the Virgen Rocio Hospital, Seville, for the study and screening of ischemic heart disease in patients eligible for high-risk cardiovascular transplantation. Consultation included a clinical assessment of the patient and ordering of appropriate cardiac ischemia tests, including invasive studies such as coronary angiography. Once they were enrolled, those patients who received transplants and those who remained on dialysis for whatever reason were monitored in the clinic.

The study protocol included the completion of a detailed clinical history, electrocardiogram, blood tests and echocardiograms for all patients. Tests for ischemia detection (Ergometry\textsuperscript{15}), Perfusion scintigraphy with Tc 99\textsuperscript{16} and Stress echocardiography with dobutamine\textsuperscript{17}) were carried out in asymptomatic patients according to clinical practice guidelines\textsuperscript{18}. Decisions were always made involving intractable lesions, poor distal vessels or very distal lesions. Surgical revascularization was indicated in patients with multivessel lesions and/or left main lesions, as outlined in clinical practice guidelines\textsuperscript{18}. Decisions were always made on consensus during meetings with both medical and surgical specialists (Heart Team).

The antiplatelet treatment used in patients who were implanted with endovascular devices (stents) was acetylsalicylic acid (ASA) and clopidogrel. Dual antiplatelet therapy was continued for 6 months in patients who received a metallic or conventional stent and for one year in patients with a drug-eluting stent. Patients were temporarily excluded from the waiting list for kidney transplantation while they were on dual antiplatelet therapy. It must be considered that the devices implanted during the first years of the study were first-generation drug-eluting stents, which is why the recommendations for dual antiplatelet therapy duration are different from current recommendations based on newer evidence.

The clinical follow-up of the patients was carried out in the same clinic cardiologist where the study was started; thus, the same clinical cardiologist monitored a
given patient's course. Patients without any evidence of heart disease were monitored annually, while those who underwent revascularization were followed up at one month, six months, and one year. The management and control of cardiovascular risk factors during follow-up was an essential component of these patients’ care. Treatment was optimized in accordance with European clinical practice guidelines; patients received ASA, statins, angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARA-II) and Beta blockers19-21.

Definitions

High cardiovascular risk of the population with advanced CKD is defined by the presence of one or more of the risk factors listed in Table 1. All the patients who were followed by our consultation service were considered to have high cardiovascular risk. Corrected age is defined as the chronological age plus the time that the patient has been on dialysis.

Significant coronary lesions are defined as those causing a reduction of >75% of the luminal diameter of an epicardial vessel (vessel with a diameter above 1.5 mm) or >50% if the location is the left main coronary22. In cases in which the angiographic interpretation was in doubt, lesions were assessed by intravascular ultrasound (IVUS) or by pressure guidewires (fractional flow reserve, FFR).

Occult coronary disease is defined as the presence of significant coronary lesions in asymptomatic patients.

Cardiac events during follow-up were defined as the appearance of an acute coronary syndrome (unstable angina or acute myocardial infarction with or without ST-segment elevation) or sudden death (unexpected death less than 1 hour after onset of symptoms). We assumed that all sudden death that was unexplained was cardiac in etiology, despite the high frequency of ion channel disorders in these patients. Vascular events refer to the occurrence of ischemic or hemorrhagic cerebral vascular accidents during follow-up.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation. Values of p<0.05 were considered statistically significant. The differences between groups were analyzed using ANOVA and chi-squared tests as appropriate. All the statistical analyses were performed with the software SPSS, version 16.0 for Windows.

Ethics statement

The authors declare that all humans involved in this study were treated in a manner in accordance with the Declaration of Helsinki and the Declaration of Istanbul. Our study was exempt from approval from an ethics’ board.

Results

From November 2005 to December 2013, we studied 313 patients candidates for kidney transplant, who underwent coronary angiography, of whom 94 eventually underwent transplantation. The demographic clinical characteristics of the study population are shown in Table 2.

Patients were predominantly male (200 of 313 (64%)) and of almost exclusively Caucasian race (99%). Hypertension was the most prevalent cardiovascular risk factor (96%). Almost two thirds of the patients were diabetic, with diabetic nephropathy accounting for almost 20% of the causes of CKD. Of the 313 patients, 39 had a prior diagnosis of ischemic heart disease (12%). The high prevalence of smoking among the study participants is striking (56%). It is important to note that 86% of participants did not have any cardiac symptoms. The most common symptoms were chest pain and dyspnea on exertion.

The mean duration of renal replacement therapy was 1.1 years (0.2 - 4.9 years), with hemodialysis being the most prevalent modality. The main causes of acute CKD (ACKD) were glomerulonephritis, diabetic nephropathy and vascular nephropathy.

The sensitivity and specificity of the various ischemia detection tests are shown in Table 3. Most tests

<table>
<thead>
<tr>
<th>Table 1. High cardiovascular risk</th>
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<tr>
<td>1.- Coronary artery disease documented</td>
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<tr>
<td>2.- Symtomatic typical angina or anginal equivalent</td>
</tr>
<tr>
<td>3.- Asymptoms patients with one of the following features:</td>
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<tr>
<td>a.- Age “corrected”(chronological age plus years corrected in SRT) above 55 years</td>
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<tr>
<td>b.- Age corrected between 35-55 years and 2 or more clasic risk factors</td>
</tr>
<tr>
<td>- Family history of early coronary artery disease</td>
</tr>
<tr>
<td>- Dyslipidemia</td>
</tr>
<tr>
<td>- Hypertension.</td>
</tr>
<tr>
<td>- Active smoking or ex-smoker of ≥10 cigarettes</td>
</tr>
<tr>
<td>- Non-coronary atherosclerotic disease demonstrated</td>
</tr>
<tr>
<td>4.-Diabetes Mellitus</td>
</tr>
<tr>
<td>5.- LVEF &lt;50%</td>
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had a lower sensitivity and specificity in patients with CKD than in the general population, except myocardial perfusion scintigraphy with pharmacological stress (adenosine SPECT), which had somewhat similar sensitivity (87% vs 88%) but lower specificity (60% vs 73%).

**Results of coronary angiography**

As shown in Table 4, the prevalence of significant coronary lesions found on catheterization was high (123 of 313 patients (39.3%)), and all lesions had some component of calcification to varying extents (diffuse lesions: 51%; focal lesions: 49%). The prevalence of occult coronary disease was 32.4%; of these, 27% had negative ischemia detection tests.

Of the 123 patients with significant coronary lesions, 83 (67.4%) underwent revascularization; most revascularization was percutaneous (96.2%), and only 4% of patients required surgical revascularization (2 patients with left main lesions and another 2 with multivessel disease and involvement of the proximal descending artery). Forty patients (32.5%) were considered non-revascularizable, either because they had technically unapproachable lesions or due to high surgical risk or poor distal vessels; for such patients, the adjustment of conservative treatment as the only therapeutic possibility. Regarding the type of stent implanted, in the first years of the study conventional stents were used (30 patients). With the later development of drug-eluting stents, these stents were implanted in 40 patients. Nine patients received a combination of drug-eluting and conventional stents.

It should be noted that complications related to catheterization were rare (<1%), and they mainly involved local complications at the puncture site (4 patients developed a pseudoaneurysm, one of which resolved spontaneously; two were implanted with stents and one required surgical closure by vascular surgery). None of the patients who were in the predialysis stage at the time of coronary angiography developed contrast nephropathy, and there were no other complications related to percutaneous revascularization in those undergoing renal replacement therap. A periprocedural infarction and a subacute restenosis of one of the conventional stents occurred, and both resolved satisfactorily. The rate of clinical restenosis of the stents was 7% (6 patients), with no differences according to the type of implanted device.
Exclusion of transplant candidates

The exclusion criteria for transplantation are shown in Table 5: severe cardiac dysfunction (LVEF<30%), especially ischemic dysfunction, the presence of significant non-revascularizable multivessel or single-vessel coronary lesions with moderate to severe ischemia on screening tests, and the presence of severe uncorrected valvular heart disease. Based on these criteria, a total of 24 patients (7.6%) were excluded; these were mainly patients who were not candidates for coronary revascularization and had severe ischemia.

Mortality analysis

Table 6 shows the mortality outcomes during follow-up (24 months ±15 months) for all patients studied in the clinic, transplant patients, and patients who underwent revascularization (regardless of whether they received a transplant). Total mortality was 10%, with cardiovascular causes accounting for half of the deaths. With regard to the main focus of the study, mortality in transplant patients from any cause was 5.3% (5 patients), with only 2 deaths of cardiovascular etiology (due to heart failure). The cardiovascular mortality of transplant patients who underwent revascularization was 0%.

Discussion

The main purpose of the study was to assess the burden of cardiovascular disease, especially ischemic disease, in our population of transplant candidates at high cardiovascular risk. We also aimed to decrease cardiovascular mortality among transplant patients, as cardiovascular disease is the leading cause of loss of a functioning allograft in our setting. The prevalence of ischemic heart disease in our study was high (39.3%); it was even higher than in the series published by Kumar et al.13, in which it was approximately 28%, but was somewhat lower than in the study by Ohtake et al.23, in which case it exceeded 50%. In addition, in more than half of the cases (54.4%), the demonstrated coronary lesions involved more than one vessel and all of them had some degree of calcification. Considering that the average duration of renal replacement therapy slightly exceeds one year, this result suggests that the progression of coronary atherosclerosis begins in stages of disease that precede inclusion in dialysis programs. Therefore, carrying out screening for ischemic heart disease at earlier stages of CKD (stage 3-4) would allow for earlier diagnosis and the initiation of an optimal treatment regimen to delay the progression of coronary disease, with pharmacological adjustment and coronary revascularization if appropriate. Early invasive management is not associated with an increase in the rate of complications inherent to catheterization, as reflected in this and other studies. The overall rate of complications did not exceed 1%. Most complications involved the puncture site, and all of them resolved without any mortality. One controversial point is the possibility that coronary angiography may accelerate the initiation of renal replacement therapy in those patients who are in predialysis stages of CKD. Kumar et al.24 found that coronary angiography screening in predialysis patients did not accelerate the initiation of dialysis. These results that are comparable to ours, as we did not observe any case of contrast-induced nephropathy or cholesterol embolization, and there was no accelerated initiation of dialysis.

In contrast to the general population, the presence or absence of anginal symptoms was a poor indicator of coronary disease in our patients, as 86% of them were asymptomatic (Table 2), but 32% in the asymptomatic
group had significant coronary lesions. This important result is in agreement with the percentage of asymptomatic patients with coronary lesions reported in a previous study\textsuperscript{13}, although the value in that study was somewhat higher (54%). The absence of symptoms cannot be explained solely by the autonomic neuropathy of diabetes mellitus, since the prevalence of diabetes in our study was 31% and diabetes was not always present in asymptomatic patients. Nor can it be explained by the prevalence of silent single-vessel coronary lesions, which accounted for less than 50% of cases in our study, or low activity level in uremic patients, as some of these silent lesions were observed in participants with good functional capacity on ergometric testing. In short, this “clinical silence” might suggest some degree of uremic neuropathy that masks ischemic symptoms.

The utility of the ischemia detection tests to screen for coronary heart disease in patients in our series is highly controversial (Table 3). Given the high prevalence of cardiovascular disease in patients with ACKD and minimal symptoms, values of sensitivity and specificity close to 80% are necessary for reasonable and safe screening. In our case, these tests were not very useful to rule out significant coronary disease, as they had very low sensitivity and therefore resulted in false negatives that were subsequently confirmed with catheterization\textsuperscript{25}.

Table 7: Predictors associated with the presence of significant coronary lesions

<table>
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<tr>
<th>Predictors</th>
<th>HR</th>
<th>CI 95%</th>
<th>P</th>
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<tbody>
<tr>
<td>Diabetes</td>
<td>3.8</td>
<td>2.8-19.2</td>
<td>0.003</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>1.8</td>
<td>1.1-12.3</td>
<td>0.045</td>
</tr>
<tr>
<td>Coronary calcification</td>
<td>18.2</td>
<td>6.3-34.3</td>
<td>&lt;0.001</td>
</tr>
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</table>

Cardiovascular risk factors.

There is not enough evidence in the general population to guarantee that preventive revascularization of asymptomatic individuals increases survival\textsuperscript{27}. However, there is also no evidence that the lack of benefit can be extrapolated to patients with ACKD (stages 4-5), those at high cardiovascular risk, or candidates for kidney transplantation with a high rate of cardiovascular mortality. The data from the Andalusian Registry of Chronic Kidney Disease “SICATA 2010-2011” that served as a reference in the analysis of mortality show that cardiovascular disease is the first cause of death for patients on any renal replacement therapy. In a British registry, the reported cardiovascular mortality of transplant patients was 16%\textsuperscript{26,29}, while in the US Renal Data System, it was 30%\textsuperscript{26}. In general, our results are very different from these figures, as our population had lower cardiovascular mortality overall (4.8%) and specifically in transplant patients (2.1%) (Table 6). These data can be applied to other groups in which invasive ischemic heart disease screening was performed\textsuperscript{13}, with cardiovascular mortality of 3.3%. Whereas Kumar et al. reported 1.9% mortality in transplant patients who underwent revascularization, our group did not document any cardiovascular death in this population during follow-up.

Finally, and to highlight the safety of coronary intervention in the overall study population, regardless of kidney transplantation, of the 83 procedures that were carried out (4 surgically and 79 percutaneously), we observed only one subacute stent thrombosis in the first month and 5 late clinical restenosis in dialysis patients, which resolved favorably. Therefore, given the technical advances in revascularization, the availability of new-generation stents and dual anti-platelet treatments and the ability to modulate risk factors during follow-up, coronary intervention seems to be beneficial in patients with ACKD.

Conclusions

In conclusion, the exclusion of patients with severe cardiac pathology (Table 5) and the use of medical and invasive coronary interventions contribute to the reduction of cardiovascular mortality in transplant patients. As a result of these interventions, as of 2015, cardiovascular disease was no longer the primary cause of death in transplant patients or in patients undergoing renal replacement therapy in our hospital. The main limitation of our study
is that it is observational at a single center, such that direct comparison with another group is not possible. However, the results obtained are similar (and in some respects superior) to those of other studies in which invasive screening for ischemic heart disease was performed in pretransplant patients, and cardiovascular mortality was reduced without increasing the number of complications inherent to angiographic studies. Nevertheless is necessary follow-up studies and the clinical daily life to confirm these results.

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