MÉDICAS UIS
REVISTA DE LOS ESTUDIANTES DE MEDICINA DE LA UNIVERSIDAD INDUSTRIAL DE SANTANDER

Revisión de tema

Is there evidence for an early start on renal replacement therapy in patients with higher glomerular filtration rate?

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SUMMARY
There is a trend in the last decade for an increase in early initiation in renal replacement therapy in the United States. In 1996 19% of patients initiated dialysis with an estimated glomerular filtration over 10 ml/min/1,73m2 percentage that actually has increase to 45%. This review will show the reasons and evidence behind the current tendencies. There is no factual evidence to support the claim of the beneficial effects in early dialysis starts. Data so far shows increase mortality in early dialysis, unrelated to the co-morbidities of patients with advanced chronic kidney disease. Residual renal function could also be affected by early initiation of dialysis, hampering survival in the long run. Finally will be showing the financial burden to the health system. Randomized clinical trials are needed to answer these questions. (MED.UIS. 2009;22(3):222-6).
Key words: Hemodialysis. Chronic renal failure. End stage kidney disease. Renal replacement therapy.

Introduction

Chronic Kidney Disease (CKD) has an increasing incidence and prevalence. Especially with a prevalence of diabetic patients in the United States that exceeds 40 % as shown in the renal registry of the United States Renal Data System (USRDS). The question of how and when to start dialysis should be delayed, particularly when the patient is still asymptomatic. Many times this is not feasible due to the "catastrophic" start of some patients, referring to patients who did not have a good follow up with a nephrologist with a suitable plan for the creation of a vascular access for dialysis, appropriate treatment of anemia, blood pressure control and the mismatch in bone mineral metabolism due to renal disease and nutrition. Absolute indications for the start of Renal Replacement Therapy (RRT) are: uremic pericarditis or pleuritis, encephalopathy or neuropathy, bleeding, hypervolemia refractory to diuretics, acid-base and electrolyte abnormalities refractory to conventional therapies, persistence of nausea and vomiting and signs of malnutrition with weight loss. Regarding indications based in the use of formulas of Glomerular Filtration Rate (GFR) in the year 2006 guidelines from the National Kidney Foundation Dialysis Outcomes Qualitive Initiative were issued recommending the start of RRT in patient with CKD stage five (GFR < 15 mL/min/1,73m^2). The initiation of dialysis before the above mentioned parameters is going to depend on the patient's clinical status. In Europe in the year 2005 the European Best Practice guidelines for Peritoneal Dialysis recommended dialysis with values of GFR below 6 mL/min/1,73m^2, considering an early start with values between 8-10 mL/min/1,73m^2 of GFR. In this review we will show the controversies arising in the medical literature regarding the early initiation of dialysis in patients with CKD stage five and above, emphasizing the economical and clinical impact the decision entails. Similarly it is shown if this early start is damaging from the clinical and survival stand-point of view.

When to start dialysis?

It is difficult to establish the ideal timing for the initiation of dialysis in patients with CKD. Diverse research groups have tried to answer this question based on cohort studies and case series[1]. These researchers advocate that early initiation of dialysis with elevated values of GFR will improve morbidity,

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Artículo recibido el 16 de septiembre de 2009 y aceptado para publicación el 25 de noviembre de 2009

mortality, employability and quality of life. However the clinical studies mentioned are subject to various statistical "confounding factors", like the delay in referral to a specialist, age of the patient and other co-morbidities. Therefore there is no definite conclusion for the ideal time to initiate RRT. A recent cohort study recommends randomized clinical studies to answer this question, but probably these studies will never take place[2]. Despite lack of evidence, expert panels of different countries have issued practice guidelines that recommend the start of dialysis at levels of GFR above the usual parameters. The adoption of these recommendations might bring a financial burden to our health systems and dialysis services. Data concerning these practices have been documented in United States, Australia and New Zealand[3]. It will be necessary, in the near future, to perform randomized controlled clinical trials that will evaluate the economic cost and the prognosis of patients subject to early start of RRT. Making an analysis of the data extracted from the USRDS it can be seen that there has been an increase in the number of patients who started dialysis (both hemodialysis and peritoneal dialysis) with GFR above 10 ml/min/1,73m^2[4]. (Figure 1). In the year 1996 15 % of these patients who started RRT did it with GFR between 10-14,9 ml/min/1,73m^2, ten years later, in 2005, this percentage increased to 30 % and 15% started with a GFR above 15 ml/min/1,73m^2. Similar observations were documented in 2007 especially in patients with eighty and ninety years of age[5]. The above observations generate the following questions: what is the potential impact of this change in current practice regarding mortality and morbidity in dialysis? What factors led to this change? What are the implications of these observations in the incidental dialysis patient and the economic burden attached to them?

THE IMPACT OF EARLY START ON RENAL REPLACEMENT THERAPY

The decision to start RRT in patients with end stage renal disease is based on presenting symptoms and baseline residual renal function (RRF) values. Some researchers have found that 23 % of the population of the US with end stage kidney disease (ESKD) started dialysis with a GFR below 5 mL/min/1,73 m^2 between 1995 and 1997[6]. In year 1997 the National Kidney Foundation published recommendations based on the existing literature at the time. They established that the start of dialysis was based on an arithmetic median equation of the blood urea and the creatinine clearance below 10,5 mL/min/1,73 m^2 not including asymptomatic patients without protein malnutrition. One of the studies that initially supported these recommendations was the Canusa study, a multicenter prospective cohort of incident patients on Peritoneal Dialysis (PD) performed in North America, designed to determine the association of membrane transport type with patient and technical survival while controlling for demographics, clinical variables, nutritional status, and adequacy of dialysis. This observational study suggested a clinical benefit regarding the preservation of creatinine clearance with values of weekly peritoneal dialysis clearance of more than 70 L/1,73 m^2[7]. Further studies, including the ADEMEX, which was a large scale prospective, randomized, controlled, clinical trial performed in Mexico evaluating the effects of increased PD small-solute clearances on mortality rates among patients with ESKD who were being treated with continous ambulatory PD, questioned these results[8]. Conclusions that were ratified in the HEMO study, a prospective, randomized, multicenter, clinical trial designed to examine the effects on clinical outcomes of two treatment parameters: urea and middle molecules clearance utilizing low and high-flux dialysis[9]. Both studies demonstrated the lack of clinical improvement (survival) with more elevated clearances of urea and serum creatinine in conventional dialysis. In the CANUSA study the improvement in survival in peritoneal dialysis patients was attributed to the existence of a more residual kidney function. If the indications by the National Kidney Foundation are followed closely and implemented, the risk of strictly using these parameters and initiating patients on dialysis in an arbitrary manner is patent. Additional publications were unable to show clear benefits for early start of dialysis. Some clinical studies have recommended premature start but presented confounding statistical errors regarding survival analysis[10].

The observational study by Korevaar, did not show advantage regarding survival, in early RRT initiation[11]. Traynor showed an increase in mortality in an observational study in Europe[12]. After adjusting all co-variants, early dialysis initiation, with GFR more than 10 mL/min/1,73m^2, is associated with increased mortality[13]. Other studies, using a multivariant Cox model, have corroborated these data yielding risk of death with each increase of GFR of 5 mL/min/1,73 m^2 at the beginning the dialysis. The confounding factors associated to this risk are the possible relationship between low levels of creatinine and muscle mass reduction or changes in body mass index in reference to the percentage of body fat[14]. As we all know dialysis patients have a marked risk of cardiovascular mortality. If we compare the population on dialysis between the ages of 64-75 years (data extracted from USRDS), the ones that began with a GFR between 5-9,9 mL/min/1,73m^2 presented a mortality rate during the first year of 25 % that contrasted with the patients that started dialysis with a GFR of more than 15 mL/min/1,73 m^2 with a mortality of 41,5 %. The relationship between increase mortality and elevated GFR at the initiation of dialysis has statistical value that persists after including confounding variables such as age, sex, race, and co-morbidities (including

diabetes). This analysis was based on 900 000 patients from the USRDS between the years 1996-2005. Murtagh et al showed in his retrospective studies that patients older than 75 years with CKD stage five did not yield substantial differences in co-morbidity if they were receiving RRT or non-dialytic medical therapy by a nephrologist[15].

What are the causes behind an early start of dialysis?

Various hypothesis have been postulated to explain the actual tendency for early initiation of dialysis: too much reliance in GFR equations rather than initiation of RRT based on clinical findings, lack of understanding of the recommendations for the proper use of GFR or creatinine clearance formulas and the adequate implementation in the decision to start dialysis. Management of the different types of CKD complications like hypertension, volume overload, and anemia through dialytic techniques instead of pursuing non-invasive conservative measures, and the start of RRT based on signs of malnutrition (hypo-albuminemia) as well as monetary reasons among other causes. This last hypothesis is difficult to prove since the same tendency for early starts have been found in countries without financial incentives like the United Kingdom. In the United States, after analyzing the data of the USRDS between the period of 1995-2006, there are similar tendencies for the start of dialysis based on equal GFR parameters in both subsidized and private dialysis units. It is very difficult to pinpoint the reason behind this early starts. The lack of randomized clinical trials does not support these tendencies. Hopefully the IDEAL study, a three year multicenter, prospective, randomized controlled performed in Australia and New Zealand that will asses the effect of commencement of dialysis at two different GFR levels on patients outcomes, will shed light in this matter soon[16].

Is it harmful to start renal replacement therapy earlier?

There is lack of evidence regarding the benefit of early start of dialysis. Clearly, it is important to preserve RRF in patients on RRT[8]. The preservation RRF allows the use of dialysis with low clearances. The CANUSA study showed important associations between residual renal function at the beginning of dialysis and the nutritional status of the patient[17]. Another consideration is the fact that patients older than 75 years old have a tendency of lower decrements in RRF and increased mortality when they reach CKD stage four[18]. Therefore the early start of dialysis in these patients with preserved residual renal function may be deleterious due to the fact that dialysis can deteriorate RRF faster due to hemodynamic changes increasing mortality as well[19]. Not to mention the complications derived from the inappropriate use of vascular access in this population, which can lead to infection among others. A Cohort study performed on nursing home patients, after initiation of hemodialysis, using data obtained from the USRDS, showed marked decline in functional status during the period surrounding the initiation and by one year after the start of dialysis. Findings suggested that in most nursing home residents with ESKD, functional decline continous despite initiation of dialysis. However, the study fails to explain why the decline in functionality despite the treatment of uremia, taking in consideration the high prevalence of disability at baseline, coexisting medical conditions, hospitalizations, physical risks associated with the dialysis technique, and the consideration that "kidney disease" may be a reflection of terminal multiorgan failure rather than a primary cause of functional decline[20]. It is still unknown the trends leading this "fashion" of early start of dialysis. Maybe it is based on the interpretation, perhaps incorrect of guidelines promulgated by different government agencies. Guidelines that are based on retrospective and observational studies and lack good randomized clinical trials as mentioned before.

The effects of early dialysis start in the incidence and financial cost of renal replacement therapy

The phenomenon of early start of dialysis in patient with GFR above 10 ml/min/1,73m^2 could have influenced the increasing costs of Medicare-IRC in the United States. Marked increase noted in the period between 1996-2005. In 2006, the average/yearly cost of dialysis treatment in patients older than 65 years was 71 000 dollars. In 2005, 18 076 more patients initiated dialysis than in 1996. Additional studies are needed to assess the possibility of the arbitrary use of GFR equations by nephrologists in order to decide when to start RRT in our patients. Obviously when indications to start dialysis are present (encephalopathy, uremic pericarditis, diuretic resistant congestive heart failure, malnutrition) there is no doubt should be implemented. However a conservative attitude (no dialysis), especially in the elderly population with multiple comorbidities and with short life-span, represents a better option. Some studies suggested this approach, with a similar survival to RRT patients[21]. There is an inherent concern in the trend of early start of RRT. There is also the need to design a randomized clinical study to answer the paradigm of early or late initiation of RRT and its impact on morbidity, mortality, and quality of

life in these patients.

Conclusion

The effects of the "rising tide" on early initiation of dialysis is viewed with concern, as it may not be justified on the basis of the risk/benefit relationship. Efforts should be undertaken now to study the phenomenon further with particular emphasis on the stability of estimated GFR (eGFR) in CKD stages 4 and 5. Specifically, a US study of the impact of early versus late start of dialysis (using eGFR as a discriminating variable) on morbidity, mortality, and quality of life in the pre and post dialysis periods could be undertaken. This study would differ from the IDEAL protocol in that all subjects would be randomized at the early start (relative to RRF) to thrice weekly dialysis or to thrice weekly assessments and non-dialytic medical interventions to balance the benefits of a thrice weekly health assessment in a dialysis program.

Since 1996 there is an upward trend for early start of dialysis. The reasons are not obvious and deserve accurate studies as mentioned. The basis for starting dialysis early (eGFR over 10 mL/min/1,73 m^2) may be fundamentally flawed, because recent studies do not support a positive relationship between dialysis clearance as an additive contributor to a patient's overall renal function and to outcomes on dialysis treatment. It is clear that the most actual literature does not support early initiation due to the lack of data regarding renal and patient survival. In fact, early start causes an accelerated loss of RRF with detriment to the survival and we all know the epidemiological link that exists between preservation of RRF and survival in dialysis patients[18]. Until further studies are published, the community of renal physicians and nurses cannot recommend the early start of dialysis except in the cases listed above. The principal of "first do no harm" should be applied in our population with all its consequences.

Resumen

¿Existe evidencia para el inicio de terapias renales sustitutivas a niveles de filtrado glomerular elevado?

En los Estados Unidos se está notando un incremento del inicio precoz de terapias renales sustitutivas en esta última década. Del 19% de pacientes que iniciaron diálisis con filtrado glomerular por encima de 10 ml/min/1,73m^2 en 1996 se ha pasado a un 45%. La presente revisión pretende hacer hincapié en este fenómeno, presentado evidencia referente a ello. No se conoce si existe beneficio alguno para el comienzo precoz de diálisis. Los datos demuestran un incremento de la mortalidad en diálisis precoz que no parece ser debido a las morbilidades de los pacientes con insuficiencia renal crónica terminal. La función renal residual se puede afectar durante la diálisis de inicio comprometiendo la supervivencia del paciente a largo plazo. Finalmente, se expone el posible gasto financiero que esta tendencia acarrea a nuestro sistema de salud. Son necesarios estudios clínicos aleatorizados que den respuestas a estos dilemas. (MÉD.UIS. 2009;22(3):222-6).

Palabras clave: Hemodiálisis. Insuficiencia renal crónica. Insuficiencia renal crónica terminal. Terapia renal sustitutiva.

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