

Incremental Hemodialysis - A Transition from Conservative Treatment to Renal Replacement Therapy - The Potential in Preserving Residual Renal Function

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Abstract

The 3 sessions/week hemodialytic regimen became a standard of care about 50 years ago, as it was considered optimal for hemodialysis administration. The latest guidelines of KDOQI-*Kidney Disease Outcomes Quality Initiative*, in case of deterioration of the clinical condition, recommend the initiation of dialysis with higher levels of glomerular filtration ($< 15\text{ml/min}/1.73\text{m}^2$) compared to previous recommendations. As a result, a greater percentage of patients may actually start dialysis treatment with higher residual renal function, only because they experience a clinical deterioration. In patients with a significant decrease in residual function (residual urea clearance (RUC) $< 2\text{ml/min}/1.73\text{m}^2$) KDOQI

advises a minimum treatment of 3 hemodialysis (HD) sessions per week. In patients with significant residual function (RUC $> 3\text{ml/min}/1.73\text{m}^2$) the guidelines indicate that the HD regime 2 times/week can be applied. Incremental dialysis is the process of limiting dialysis dose at the initial onset of treatment to provide a more gradual transition toward a standard 3 sessions weekly dose. This regimen may be advised when the RUC exceeds $3\text{ml/min}/1.73\text{m}^2$, based on the ability to achieve an efficient HD treatment with 4 h/session, but should be changed if the RUC falls below $2\text{ml/min}/1.73\text{m}^2$. Incremental HD may be useful for preserving native kidney function, which is not simply a diuresis preservation, but is

associated with significant benefits in terms of volume control, solute clearance and elimination of uremic toxins.

Keywords: residual renal function, incremental hemodialysis, twice-weekly

INTRODUCTION

Residual renal function and the rationale of incremental dialysis

The incremental regimen of HD, which consists in the adjustment of frequency and dose of HD according to the degree of residual renal function (RRF), may be useful for preserving native kidney function in patients starting dialysis treatment (1-5). The mechanism behind this rationale, is that hemodialysis itself induces a loss of RRF of the native kidney due to: ischemic insult caused by intradialytic hypotension and post-dialytic hypovolemia, release of nephrotoxic inflammatory mediators during the procedure, reduction of circulating urea leading to reduction of osmotic diuresis and deactivation of the remaining nephrons (6,7). Some studies have shown that residual native kidney function can be preserved in patients on dialysis treatment, respectively in 70 percent after one year, 20 percent after 3 years and 14 percent after 5 years from the time of HD start (8). Several other studies have shown that patients on HD experience a more rapid decline of native kidney function compared to patients on peritoneal dialysis (PD) (9). Other studies suggest that frequent HD sessions accelerate the decline of RRF. In a group of patients from the study "Frequent Hemodialysis Network Nocturnal Trial" of non-anuric patients, those with a high-frequency dialysis treatment (6 times/week) experienced a more pronounced decrease of residual renal function (judged by diuresis, urea clearance and creatinine) compared to those with

the conventional regimen (3 times/week) over a 4 and 12-months follow-up (10). The more pronounced decrease of glomerular filtration rate (GFR) in this group is thought to be related to ischemic kidney damage. Preservation of RRF is not simply a diuresis preservation, but is associated with significant benefits even in patients with dialysis treatment (in terms of volume control, solute clearance and elimination of uremic toxins) (11). Its preservation may reduce the likelihood of large interdialytic weight gain, resulting in a reduction in the rate of ultrafiltration required and avoidance of intradialytic hypotension and the so-called "stunning" of the myocardium (8,12,13,14). Small interdialytic weight gain may lead to better fluid balance and reduce left ventricular hypertrophy (LVH) and its associated cardiovascular morbidity and mortality (15). On the other hand, high and medium molecular weight solutes clearance is improved, and the serum phosphorus is better controlled (14,16,17). This means more opportunities for diet liberalization resulting in an improved nutritional state and a better quality of life (1). Furthermore, preservation of RRF may be associated with improvement in the inflammatory state, improvement in anemia parameters and decreased need for erythropoietin-stimulating agents (ESA) (18). The relationship between RRF and clinical outcomes was observed in a cohort of 734 incident HD patients included in the CHOICE study, where an association between diuresis > 250 ml and better quality of life was

found. In a subgroup of 579 patients with diuresis > 250 ml over one year, a 30% risk reduction was found for all-cause mortality, as well as a trend toward decreased cardiovascular mortality (18). Another study, including 6538 incident HD patients, tested the association of 1-year RRF change with survival (19). The authors found that higher residual function was independently associated with better survival. They also noticed a gradient of association between the degree of renal function loss and mortality risk. Thus, the drop in GFR by 6 ml/min/1.73m² and 3 ml/min/1.73m² per year was associated with respectively 2 and 1.5-fold higher mortality, while in patients with no change or with an increase of 3ml/min/1.73m²/year in GFR, it was found a respective decrease in mortality risk by 19 percent and 39 percent (19). In another study, residual function was found to be a protective factor against the risk of atherosclerosis (20).

The concept of incremental dialysis was first described in peritoneal dialysis (PD) patients, in whom RRF served as a guide to determine the dialysis regimen (21,22). The prescription of PD is escalated dynamically, according to an individualized regimen. The determination of the target total weekly clearance takes into account native kidney function and dialytic clearance. Similarly, the evaluation of the efficiency of HD should include the duration, dose and frequency of HD as well as the residual function of native kidneys (23). A number of studies have evaluated the relationship between incremental HD regimens (once and twice/week) with

preservation of RRF (24-27) and mortality (25-30).

CLINICAL STUDIES FOCUSED ON THE RELATIONSHIP BETWEEN RESIDUAL RENAL FUNCTION AND CARDIOVASCULAR DISEASE PROGRESS

A number of studies are focused on the relationship between RRF and CVD. In a study of 74 prevalent HD patients, the rate of GFR decline was compared between the twice sessions/ week regimen group and the 3 sessions/week dialysis regimen group (24). After a 18-month period, patients on the twice/week hemodialytic regimen had a slower rate of glomerular filtration decline. The study did not take into account socio-demographic differences and comorbidities in the studied population. Another study conducted in 85 incident patients on HD compared the trajectory of change in RRF (determined by diuresis measurement) between patients who started and continued HD on a twice/week regimen for longer than 6 months, versus patients who started and continued on a HD regimen 3 sessions/week during the study period. At the end of the 1-year follow-up, the proportion of patients who lost residual function was lower and the time to loss was longer in the twice/week regimen group compared to the 3 sessions/week regimen. It is important to note that GFR at the beginning of the study was higher on the twice/week regimen group. In a subgroup of 48 incident HD patients (treated for over 12 months), with urine output > 500 ml/day, the odds ratio of RRF loss

for each additional HD treatment per week was 7.2 (25). A larger study, undertaken in a population of 8,419 incident patients on HD, tested the preservation of residual renal function over 1 year with the incremental HD regimen (defined as 2 HD sessions/week, for at least 6 consecutive weeks, during the first 3 months of the study) compared to the conventional regimen (defined as 3 HD sessions/week). Approximately half of the patients who survived the first year had sufficient residual function to qualify for a twice/week hemodialytic regimen, but interestingly this regimen was prescribed in only 2 percent of patients. Patients with an incremental dialysis regimen had a slower decline in residual

function over the study time, adjusted in multivariate models. Incremental hemodialysis patients had 16 percent and 15 percent higher RUC and urine output, respectively, in the second quarter of follow-up period, and these differences persisted throughout the other quarters until the end of the study (26). Addressing concerns about adverse events, a small multicenter randomized trial including 140 patients followed up for 1 year that twice- and 3-times/week HD had comparable inflammatory, nutritional and adverse events status. Twice/week regime was associated with better QOL (31). The data of the main studies concerning RRF preservation are summarized in table 1.

Table 1. Summary of several studies concerning the effect of incremental HD on RRF

Study subjects	Author/year	HD frequency	Results
48 incident HD pts	Murea M et al./2021[27]	2 versus 3 sessions/week	Twice/week HD regimens confers better preservation of RRF.
8419 incident HD pts	Obi et al./2016 [26]	2 versus 3 sessions/week	Twice /week HD regimen was associated with better preservation e RRF
85 incident HD pts	Zhang et al./2014 [25]	2 versus 3 sessions/week	Twice /week HD regimen was associated with better preservation e RRF
74 prevalent HD pts	Lin et al./1999 [24]	2 versus 3 sessions/week	Twice /week HD regimen was associated with better preservation e RRF

IMPLEMENTATION OF INCREMENTAL HEMODIALYSIS IN PRACTICE

For the optimal implementation of incremental hemodialysis, field experts have proposed practical criteria, that can be used to identify patients who are suitable and will benefit from initiation of incremental RRT (see Figure 1). The criterion of the presence of urinary volume > 500

ml/day is important considering the potential risk of marked increase in interdialytic weight and volume overload, which may accompany the incremental regimen. To qualify for incremental hemodialysis, experts advise that patients must meet at least 5 of the following 9 criteria: 1) fluid retention < 2.5kg or < 5% of ideal dry body weight for 3-4 days without dialytic treatment; 2)

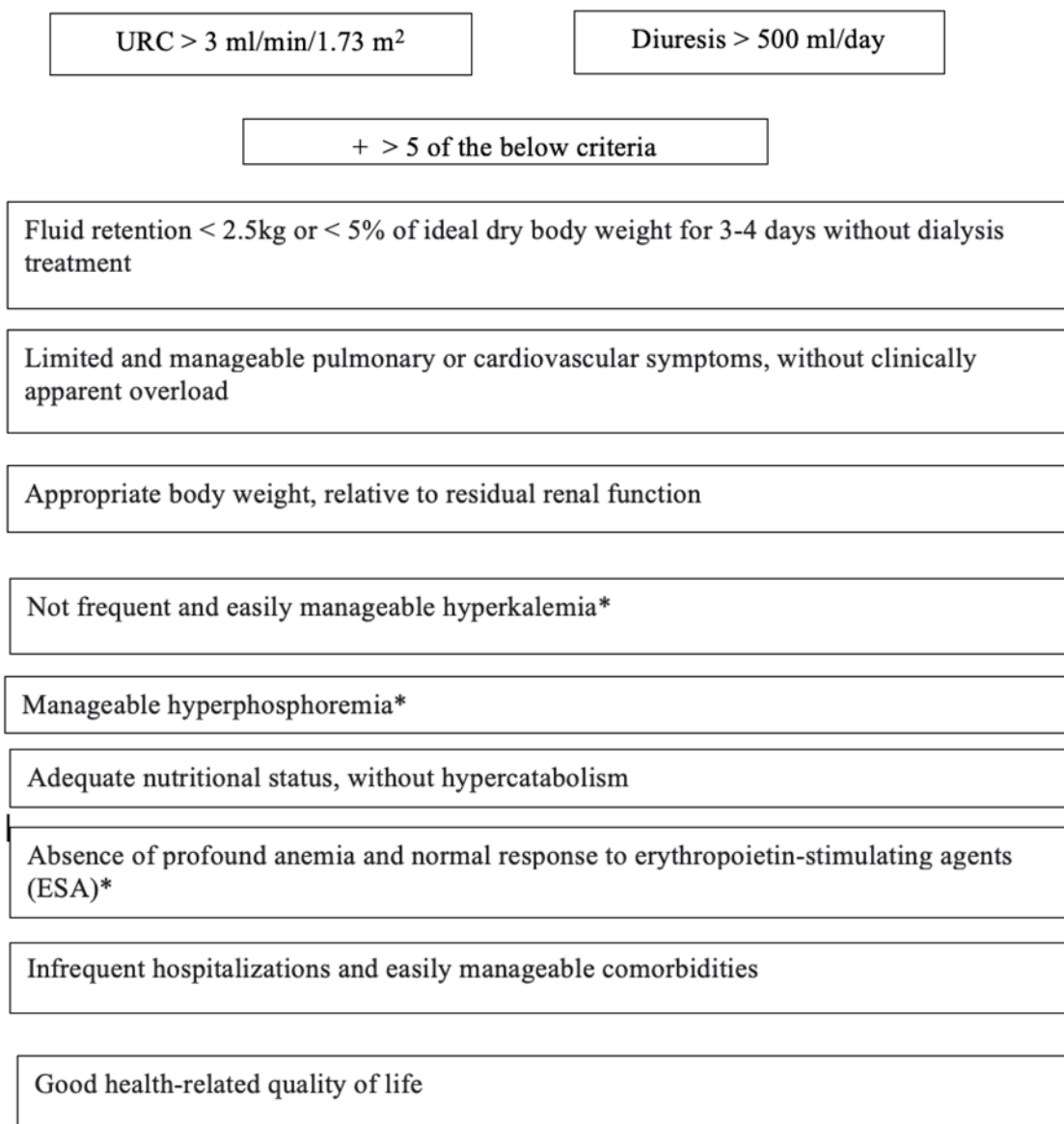


Figure 1. Proposed criteria for implementing incremental HD (2,4)

* for definitions refer text

limited and manageable pulmonary or cardiovascular symptoms, without clinically apparent overload; 3) appropriate body weight, relative to residual renal function (eg, large patients may be suitable for the twice/week regimen if they are not hypercatabolic); 4) not frequent and easily manageable hyperkalemia (defined as serum potassium $> 5.5\text{mmol/l}$); 5) manageable hyperphosphoremia (defined as serum phosphorus $> 5.5\text{mg/dl}$); 6) adequate nutritional status, without hypercatabolism; 7) absence of profound anemia (defined as HGB $< 8\text{g/dl}$) and normal response to erythropoietin-stimulating agents (ESA); 8) infrequent hospitalizations and easily manageable comorbidities; 9) good health-related quality of life (2,4).

It should be emphasized that frequent assessment, at least every 3 months, of residual renal function is very important. Residual renal function will inevitably decrease over time, rendering it impossible to compensate for infrequent HD sessions. Under these conditions, the frequency of dialysis will be increased as needed. The transition time to the 3 sessions/week regimen is determined individually based on routine assessment. As for cost implications, out of all the modalities, hemodialysis remains the most expensive treatment. In USA it is reported that hemodialysis treatment accounts for approximately 7.2% of Medicare fee-for-service spending (32). Although considerable amount of retrospective data suggests the benefit of

initiating incremental HD and feasibility is supported by several pilot studies, randomized controlled studies are required to fully evaluate every aspect of this approach including efficacy, safety, implementation and cost advantages (27).
CONCLUSION

Hemodialysis itself induces a loss of residual renal function of the native kidneys. Preservation of RRF through incremental dialysis is not just and only about diuresis preservation, but is associated with significant benefits such as better volume control, solute clearance and elimination of uremic toxins, resulting in decreased cardiovascular morbidity and mortality. Incremental hemodialysis is associated with improved nutritional state and a better quality of life. Furthermore, incremental HD is potentially associated with improvement in the inflammatory state, anemia parameters and decreased need for erythropoietin-stimulating agents. Residual renal function will inevitably decrease over time and the frequency of dialysis will be increased as needed.

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