End-Stage Kidney Patients Require Hemodialysis Therapy Full Start

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Keywords

Hemodialysis · Incremental dialysis · Incident dialysis patients · Standard Kt/V · Residual renal function · Urine output · Urea clearance

Abstract

Recently the concept that prescription of chronic hemodialysis (HD) start should be tailored based on residual renal function (RRF) and urine output (UO) has been revived from the past and called infrequent or incremental dialysis. It mainly consists in prescribing 1 or 2 HD sessions per week instead of what has become the standard thrice-weekly HD. It is both surprising and fascinating that almost 60 years after the first end-stage kidney disease patient was treated by Scribner et al. [Trans Am Soc Artif Intern Organs 1960;6:114–122], the nephrology community still questions the best way to start HD therapy. This comforting process is the result of pieces of evidence accumulated with time such as that RRF is associated with better outcomes that starting HD therapy favors the loss of RRF and/or UO and also results in a high rate of deaths in the first weeks of HD therapy. Through this review, we support the idea that when the decision to start HD therapy is made, ideally with the full collaboration of the

patient, it is necessary to be efficient to alleviate uremic symptoms, to correct the fluid overload and to allow a full recovery from the uremic state associated with the late stages of non-dialysis chronic kidney disease.

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Historical Perspective

In a riveting preliminary report, Scribner et al. [1] analyzed the management of the first 2 patients treated for end-stage kidney disease (ESKD). Thanks to the arterio-venous shunt, the first patient was prescribed a dialysis session that lasted 76 h! This was dictated by the extreme weakness of the patient related to the severity of the uremic intoxication. The initial hemodialysis (HD) program was a once-weekly session, then switched to twice-weekly after several weeks because of the drop of residual creatinine clearance falling from 4 to 0.7 mL/min and recurrence of the uremic symptoms. In 1969, Curtis et al. [2] reported their experience with maintenance HD. Patients were treated 12–14 h twice per week. Progressively patients were switched from 2 to 3 sessions per week and at the same time the session duration decreased until the

current standard recommendation of 4 h thrice weekly [3, 4]. We will follow with a personal anecdote; 2 decades ago, we had a discussion with Guy Laurent [5], founder of the Tassin dialysis unit in France. At that time and as a legacy from the 1960s practice reported above, there still were patients in the unit under twice-weekly 10–12-h HD therapy, whereas most of the patients were under thrice-weekly 8-h schedule. The question to him was “Why did you switch patients from 12-h twice-weekly to 8-h thrice-weekly program.” His answer was: “...because we lost several patients from hyperkalemia on twice-weekly HD therapy.” This answer was striking, highlighting the hazards of the intermittence in HD therapy. Of course, the story is far from complete. Were the patients with unexpected deaths incident or prevalent? Were they anuric or still passing some urine?

Why Challenging an HD Full Start?

There are strong arguments to challenge what has become the standard way of starting HD therapy that is since the 1980s – thrice-weekly HD, 3–5 h per session. First, there is a peak of mortality and cardiovascular (CV) events in the first weeks of standard HD [6, 7]. It may be interpreted as a challenge to fragile patients by the extra-corporeal therapy with the hypothesis that less dialysis would avoid this peak. Second, the preservation of residual renal function (RRF) and/or urine output (UO) is currently an important matter of concern because persistent RRF/UO are associated with better survival, easier handling of volume status, better middle molecule and phosphate clearance, and less inflammation [8]. Standard HD is associated with a progressive loss of RRF/UO and intensive dialysis is associated with more rapid decline. Then it is hypothesized that less aggressive and/or less frequent dialysis favors RRF/UO preservation. Third, quality of life (QOL) has become an important outcome in the value of care provided to ESKD patients. It is essential in evaluating centered-patient therapies. Incremental dialysis, sparing time spent on the dialysis machine and on transportation appears intuitively associated with better QOL. Fourth, HD therapy is very costly for the patients or the community. Less frequent dialysis appears a good way to spare funds.

Before addressing more deeply the arguments supporting the incremental dialysis concept, it is necessary to state as a preamble that no randomized controlled trial (RCT) has compared incremental and standard HD when patients initiate HD therapy. The available clinical data

are not numerous and recently 16 studies were identified for a meta-analysis [9]. We will focus the debate of twice-weekly HD (incremental) versus standard thrice-weekly HD. We will not include in this discussion the Combined Dialysis Diet Program (once weekly HD and low protein diet) [10]. It is out of the scope of incremental HD therapy as recently reported by several teams.

Early Mortality in Patients Starting HD Therapy

Foley et al. [7] have reported the early peak of mortality at week 6 after HD start from a large cohort of 498,566 ESKD patients enrolled in the USRDS database between 2005 and 2009. This confirms previous reports from North America [11, 12]. Older age, catheter as vascular access, low serum albumin and low serum phosphate, cancer, and congestive heart failure were associated with elevated early mortality. However, there is no information available on the dialysis prescription, except that 6% of the patients were started on peritoneal dialysis and that 78% of HD patients had catheters as vascular access. No relationship between the initial poor outcomes and dialysis dose or loss of RRF has been clearly established. Increased mortality in the first weeks after HD starts occurs at a time when RRF is at its maximum before decline [13]. Bradbury et al. [11] identified that 20% of the early deaths were related to dialysis withdrawal, significantly lower in patients with predialysis care. However, the high mortality in the first weeks were mainly due to CV disease in an European cohort reported by Eckardt et al. [6] during the first 4 months of HD therapy. Interestingly, the composite of CV events was related to criteria of low dialysis efficiency, lower blood flow rate, and lower Kt/V. High dialysis dose was also associated with higher rate of CV events, questioning the possible bias of KT normalization by “V,” a high Kt/V then potentially a surrogate of low weight and malnutrition. Also, lower ultrafiltration was associated with a higher risk of CV events. Then, from this report, it appears that early mortality in this setting is more related to “less dialysis” than the opposite.

Does Twice-Weekly Dialysis Reduce Early Mortality of Incident HD Patients?

A recent meta-analysis has reported a risk reduction of 20% with incremental dialysis [9]. However, this remains controversial [14], without any available RCT and possible bias by indication when twice-weekly HD is implemented for economic matters or/and in patients younger

with less comorbidities as reported by Lindenfeld et al. [15]. Moreover, three of the main clinical studies found no difference on mortality between incremental and standard HD [16–18]. Even in the study by Obi et al. [17], survival at the end of the first year of HD therapy was an inclusion criterion, excluding patients deceased in the first months. Also, to completely cover the scope of early mortality, it is important to emphasize the risk related to the long interval of the weekly sequence with a higher risk on Monday and Tuesday after the long interval with also a doubled risk for admission because of congestive heart failure or for any CV events [19]. Naturally twice-weekly HD, which increases this risk per se, must be restricted to selected patients as defined by Kalantar-Zadeh et al. [20] to avoid it. However, the risk may emerge anytime despite thorough and regular evaluation when RRF declines progressively and unnoticed or abruptly because of an intercurrent event. Performing routine twice weekly HD is particularly dangerous for HD patients in unstable conditions and this is reinforced in case of partial efficiency of the therapy.

Currently, no robust data confirm that incremental dialysis decreases the early peak of mortality in incident HD patients.

Is It Possible to Reduce Early Mortality with Standard Thrice-Weekly HD?

The answer is definitely positive. Specific care programs for incident HD patients are efficient to reduce early mortality, such as reported with the Right Start and IMPACT programs [21, 22]. Recently among Nephro-Care France units we have implemented from October 2015 a Specific Oriented Care Program for HD Incident Patients (SOCHIP program). Compared to the historical mortality rate (2014–2015), the crude mortality for the 2016–2017 has been reduced from 30.1 to 22.4 deaths/100 patients/year ($p = 0.0002$) [23].

Preservation of RRF

Since more than 10 years, it is now recognized that RRF is related to HD patient outcomes [24]. RRF and/or UO are the cornerstone of the incremental HD concept [25]. Its preservation benefits the patient in several domains previously mentioned. Frequent HD Network (FHN) trials have brought important information regarding the effect of frequency and session duration on RRF. When compared to standard thrice-weekly HD, short-daily HD displayed no difference in RRF at the

end of the first year of the trial. However, only one third of the patients had a significant UO and patients with residual urea clearance >3 mL/min were not suitable for inclusion in the trial [26]. Therefore, these results must be interpreted with caution. On the contrary, the patients treated with daily nocturnal long-hour HD in the nocturnal home FHN trial [27], most of them being incident patients, presented after 1 year with a significant decline of RRF compared to thrice-weekly standard HD [26]. It then appears that the session duration impacts more significantly the RRF than the session frequency itself.

Is Twice-Weekly Dialysis Associated with a Better Preservation of RRF?

In the meta-analysis by Liu et al. [9], RRF and UO are better preserved with incremental or twice-weekly HD when compared to thrice-weekly HD. As mentioned above, only 16 studies were included in the analysis, and 7 regarding the effect on RRF and/or UO. Among the 7, there was some heterogeneity such as studies including prevalent [28, 29] and incident patients [17, 18, 30, 31]. Also one of the 7 trials combined infrequent dialysis (once weekly) and low protein diet (Combined Diet Dialysis Program) [10], a different scope of twice-weekly HD program for incident patients. Zhang et al. [31] comparing 30 twice-weekly and 55 thrice-weekly HD patients found that the loss of RRF/UO occurred, respectively, in 34 and 21 months ($p = 0.05$). However, the 2 largest studies in incident patients reported contradictory results [17, 18].

Now the evidence of incremental dialysis on RRF/UO preservation remains to be confirmed.

Why Is the Question of RRF/UO Pivotal in Incremental HD?

In the study by Obi et al. [17], the dialysis dose target estimated from standard Kt/V (2.1 per week) was met in 90% of the patients on thrice-weekly HD and twice-weekly HD with urea clearance above 3 mL/min/1.73 m². In twice-weekly HD patients below that level of urea clearance, only 30% of the patients with incremental HD reached the target, exposing the patient to insufficient depuration. Moreover, it appears clearly that RRF and UO are associated with patients' survival in the incremental program. When urea clearance was below the 3 mL/min threshold or when UO was below 600 mL/day, mortality was found significantly higher in incremental HD patients compared to thrice-weekly HD (hazard-ratios [HR] 1.61) [17].

Is RRF/VO Routinely Assessed in HD Patients?

The answer is clearly “no,” starting by our own unit. Recently Obi et al. [17] analyzed a large cohort of incident patients from a large dialysis organization to assess the initial and 5th quarter urea clearance and the effect of urea clearance decline on patient survival. Among the initial cohort (2007–2010, 67,311 patients), 22,895 patients had available initial urea clearance assessment (34%). Among those, only 6,895 patients had available urea clearance assessment at quarter 5th (29%). This demonstrates that RRF assessment is not routinely done, even in a large dialysis organization with a structured organization for care quality. Regular urine collection between 2 dialysis sessions and its coordination are cumbersome for the patient and the staff. There is also some confusion among nephrologists about the suitable indicator to assess RRF/VO: urea clearance, average urea and creatinine clearance, 24-h VO, interdialytic VO. The latest literature about incremental dialysis uses urea clearance and VO. According to recent proposals, RRF/VO should be assessed every 1–3 months to ensure that twice-weekly HD prescription does not pose a risk to patients, with thresholds of 3 mL/min/1.73 m² for urea clearance and 600 mL/day for VO [14, 32]. On a large scale, it remains a significant burden for all the stakeholders in the dialysis unit.

Incremental HD Program and Hard Outcomes

In the meta-analysis of 15 studies by Liu et al. [9], incremental HD offers a survival advantage compared to standard thrice-weekly (risk ratio at 0.80 [0.73–0.87]). Heterogeneity of these data has been underlined above. In a prospective multicenter cohort comparing 312 matched patients (107 on twice-weekly HD and 207 on thrice-weekly HD), Park et al. [18] have reported no survival difference at 12 months. In a large retrospective cohort and as previously mentioned, Obi et al. [17] have reported an increase in the risk of death when urea clearance is below 3 mL/min/1.73 m², whereas above this threshold, patients had a non-inferior risk of death. Interestingly, using more detailed data, Hwang et al. [28] analyzed prospectively mortality and morbidity in a cohort of HD patients treated for more than 3 months and divided into 3 groups: twice-weekly with RRF (VO >100 mL), thrice-weekly with RRF, and thrice-weekly without RRF. Compared to thrice-weekly with RRF, the hazard ratios for twice-weekly with RRF and thrice-weekly without RRF were, respectively, at 4.20 (95% CI 1.02–17.32) and 5.04 (95% CI 1.39–18.33). Then twice-weekly HD ap-

pears clearly inferior to thrice-weekly HD when even a small amount of RRF is present (and the criteria of an VO >100 mL/min may include many thrice-weekly patients). With patients on thrice-weekly HD without RRF as the reference, the twice-weekly group with RRF had a non-inferior risk (HR 0.84, 95% CI 0.34–2.01). Regarding hospitalization risk for CV events, twice-weekly patients had no increased risk when compared to patients with RRF under thrice-weekly HD (HR 1.44, 95% CI 0.49–4.21) and a non-inferior risk compared to thrice-weekly patients without RRF (HR 0.60, 95% CI 0.28–1.29). Then from these last data, it appears that at 1 year, incremental twice-weekly HD confers a non-inferior risk of mortality only when compared to anuric thrice-weekly patients. The patient comorbidities appear also to influence the mortality risk associated with the HD modality. Mathew et al. [16] have identified an increased risk of death under incremental dialysis compared to thrice-weekly in patients with a Charlson Index ≥5.

These data underline the complexity of the relationship between the choice of the HD modality in incident patients and the outcomes. Only a large prospective RCT will be able to address this important question.

Fluid Status, the Permanent Dilemma with Preservation of RRF

The fluid status is of primary importance for the outcome of dialysis patients and it has been proposed as a priority of dialysis adequacy [33]. Persistent fluid overload favors left ventricular hypertrophy and congestive heart failure [33] and impairs the RRF/VO [34]. In incident HD patients, remaining overhydrated during the first months of HD therapy confers a significant risk of mortality [35]. In our unit, where we have maintained a specific focus on fluid balance for more than 4 decades, the initial dehydration in the first 2 months of HD therapy is on average a decrease of $-5.0 \pm 4.5\%$ from the initial body weight [36]. This fluid removal is related to the rapid decline of brain natriuretic peptide [37] and long-term decrease of predialysis systolic blood pressure [36]. In our practice, we have never prioritized the preservation of RRF/VO because of fear to persistent fluid overload. Observational reports or interventional studies using bioimpedance, have clearly shown improvement in intermediate CV outcomes such as high blood pressure, left ventricular hypertrophy, pulse wave velocity, mitral regurgitation, paradoxical hypertension, and heart failure [38–44]. However, correcting fluid excess both in perito-

neal dialysis and HD by providing a low salt diet is a risk for the RRF/UO [45, 46]. The hazards of ultrafiltration rate are now well described, associated with increased risk of intradialytic hypotensive episodes [47] and circulatory stress including the kidneys [48], but mechanisms and thresholds, if any, remain to be examined more deeply [49, 50]. Moreover, the hazards of the initial dehydration in incident dialysis patients have not been evaluated. Tools such as bioimpedance and plasma brain natriuretic peptide level may be helpful to correct fluid overload while preserving the RRF/UO and avoiding fluid excess and side effects.

Are Twice-Weekly HD Patients at Risk of Fluid Accumulation and/or at Increased Risk of Higher Ultrafiltration Rates and Hemodynamic Instability?

Despite persistent diuresis, HD patients may present with large interdialytic weight gains, especially if the frequency of dialysis is reduced. The consequence may be the need for large UF rates in patients treated twice-weekly, with an increased risk of intradialytic hypotension, cramps, and chronic fluid accumulation. However, this risk is balanced by the UO limiting the interdialytic weight gain and UF rate that are usually equivalent or lower when comparing twice and thrice-weekly HD strategies [16–18, 29, 31]. Regarding intradialytic episodes and congestive heart failure episodes, Zhang et al. [31] did not find any difference between twice and thrice-weekly HD patients. There are no available data of direct fluid accumulation measurement with bioimpedance in twice-weekly HD patients.

Quality of Life (QOL) and the Therapy Burden Acceptance of the HD Patient

Currently, very few data are available comparing incremental and standard HD regarding QOL. In Chinese HD patients Bieber et al. [51] have reported no difference in SF-12 questionnaires between patients treated twice and thrice weekly. In a propensity-matched cohort, Park et al. [18] did not find a significant difference in the overall QOL criteria and depression index at 3 and 12 months. At least there is neither inferiority of incremental HD therapy in that domain, nor superiority of what could have been expected, because of less burden provided by incremental dialysis. Moreover, in our experience, many of the ESKD patients requiring HD therapy and starting on a standard treatment, the HD therapy has strongly relieved them from uremic symptoms like – among others

– fatigue, cramps, itching, insomnia, and anorexia. We have been unable to find studies confirming and quantifying this patient perception and specific aspects of QOL in the first weeks of HD therapy. We do not know either if patients started on incremental dialysis experience the same relief regarding uremic symptoms. Last but not least, many nephrologists experience patient refusal when increasing the dialysis dose in terms of time or frequency, and this appears to be the solution to medical problems. This risk potentially exists with incremental HD prescription, but it has not been quantified.

Other Aspects

Economics

Dialysis therapy consumes an important share of healthcare funding. We lack precise data comparing both HD strategies. Theoretically, incremental HD may save expenses compared to standard HD during a certain time because of less frequent sessions to be reimbursed and less transportations to the dialysis unit. However, there might be temptation with an incremental dialysis program to start HD earlier than recommended. Also, the transition period from twice- to thrice-weekly HD may be problematic because of insufficient dialysis dose or fluid overload with increase in hospitalizations, which could escalate significantly the cost of this strategy.

Vascular Access

Because the short daily Frequent Hemodialysis Network trial has reported a 78% increase of vascular access interventions with 6-weekly short HD sessions compared to standard HD [52], several papers point out a presumed advantage of better or potentially better vascular access longevity with incremental HD, compared to standard HD [9, 16, 32, 53]. Presently there is no evidence that twice- or thrice-weekly needle insertions make a difference in the vascular access longevity.

Nutrition

Uremic toxins contribute to loss of appetite [54] and leptin is one of them [55]. Starting thrice-weekly HD therapy triggers a significant increase of serum albumin and normalized Protein Nitrogen Appearance (nPNA) [56]. In our experience, with thrice-weekly HD and even longer dialysis sessions, many patients gain body weight after the initial phase of fluid overload correction [57, 58]. These observations demonstrate that alleviating the uremic state has a positive effect on nutritional parameters

Table 1. Twice-weekly HD therapy: scope of questions and concerns

Findings to be confirmed by an RCT	Unanswered questions	Reasonable concerns
Superiority or non-inferiority in survival with twice-weekly HD	The role of early loss of RRF/UO on the early death	Early start of HD dialysis when incremental HD is planned
Increased mortality with twice-weekly HD compared to thrice-weekly HD with UO >100 mL/min	Improvement of early mortality with twice-weekly HD	Excessive staff and nephrologist workload
Better preservation of RRF/UO	Better vascular access longevity	Insufficient depuration
Long-term decrease of nPNA with twice-weekly HD	Funds sparing with twice-weekly HD	Patient refusal to switch to thrice-weekly
Non-superiority of twice-weekly HD in QOL	Improvement of well-being after dialysis start in all strategies	Reluctance of the patient to urine collection
Equivalent intradialytic hemodynamic stability	Improvement of nutritional markers after HD start	Uncontrolled fluid overload
No increase in heart failure episodes	Objective fluid status assessment using bioimpedance	Need for high ultrafiltration rates and its consequences
	Which protein diet to recommend to the patient under twice-weekly HD	

HD, hemodialysis; RCT, randomized controlled trial; RRF, residual renal function; UO, urine output; nPNA, normalized protein nitrogen appearance; QOL, quality of life.

when compared to pre-dialysis CKD5 stage, at a time when renal function and UO are even higher than days or weeks after HD onset. Such data are missing with incremental dialysis. Moreover, Hwang et al. [28] have reported a significant late decline of the nPNA in twice-weekly patients after 2 and 3 years when compared to anuric and RRF thrice-weekly patients. In a large and matched cohort of twice and thrice-weekly HD patients, Wang et al. [59] have found no difference in survival when patients are categorized by serum albumin and creatinine. This study shows how important the nutritional status is and its potential confounding effect when analyzing outcomes.

Which Patients Are Suited for Incremental HD Program and for How Long?

Kalantar-Zadeh et al. [32] have proposed 11 criteria to screen incident patients suitable for incremental HD initiation. Two are mandatory (UO > 600 mL/min and urea clearance >3 mL/min) and to be suitable, 5 additional criteria among the remaining 9 are required. These criteria must be checked regularly every 1–3

months because some of them are potentially fast-moving targets such as pre-dialysis levels of potassium and phosphate and fluid gain. This represents a large workload for the nephrologists and the dialysis staff. Chin et al. [60] while checking urea clearance in a retrospective cohort of 410 patients, identified 53% suitable for twice-weekly HD. In another recent review, Fernandez-Lucas and Teruel [61] have shown that 76% of incident patients in their dialysis unit during 2014–2015 started HD therapy with twice-weekly sessions. After 24 months, 35% of them were still on twice-weekly HD. In a group of 30 incident patients on twice-weekly, Merino et al. [62] have reported that 50% of the patients were switched to thrice-weekly HD before 1 year. In another retrospective study from the University of California Irvine, 8 out of 13 (62%) patients needed to be switched to thrice-weekly HD in an average of 8 months. In a much larger setting (434 incremental HD patients), 36% of the patients were switched to conventional HD in an average of 3 quarters [16].

These data indicate that a significant number of patients who started on incremental dialysis needed to increase the dialysis frequency several months after HD onset.

Conclusions

There are strong arguments to support twice-weekly HD as a start for ESKD management. However, the level of evidence is scarce. There are currently many unresolved issues and fears to refrain the enthusiasm regarding this new concept (Table 1). An RCT is urgently needed before this method is proposed as a new standard for incident ESKD patients. One trial comparing twice-weekly and standard thrice-weekly HD is currently recruiting participants in Spain (Dr. Fernandez-Lucas, www.ClinicalTrials.gov, NCT03302546). However, we must remain cautious. We think that routine is the worst enemy of the dialysis patient. Incremental dialysis requires a very high level of commitment from the nephrologist, the dialysis unit staff and – of course – from the patient who must be adequately informed that, if choosing this dialysis mode, at a certain time his/her treatment will have to be increased in frequency and even in session length. We must never forget the lessons of the RALES

trial, the RCT that has demonstrated the benefits of spironolactone among the patients with heart failure [63]. Subsequently to this RCT, Juurlink et al. [64] identified the expected sharp rise of spironolactone prescription for heart failure but also the important rise of hospitalization and deaths because of hyperkalemia. The explanation is that the RCT and clinical care in the real life have different perspectives. The inclusion criteria of the RALES study were overlooked by the prescribers, especially regarding GFR and combination therapies. We strongly fear that a large implementation of incremental HD may increase the risk for critical situations in many patients because of faulty treatment qualification or because of insidious changes in their own situations especially regarding RRF and/or UO. Importantly, we strongly believe that the safety and benefits of thrice-weekly HD therapy in incident patients outweigh the potential advantages of incremental dialysis. Strong efforts are needed to implement specific programs to decrease early mortality and to fight for the preservation of RRF and/or UO.

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