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DOES SHORTER HEMODIALYSIS INCREASE THE RISK OF DEATH?

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SUMMARY – Improvement in technology has made it possible to deliver a high dialysis dose in a shorter period of time. Studies of the relationship between dialysis treatment duration and mortality have revealed that the risk of death increased significantly as the treatment time was reduced. The longer duration and increased frequency of dialysis achieve an excellent clearance of small- and middle-weight toxins, enable equilibration of tissue and vascular compartments, improve appetite and permit liberalization of diet, while gentle ultrafiltration allows for better control of hypertension. Better clearance of uremic toxins, normalization of cellular and extracellular volume, and improved nutrition result in a significant decrease in morbidity and mortality of dialyzed patients. With most of dialyzers in use, adequate hemodialysis can be delivered in 4 to 5 hours, especially in a setting of maximal blood and high dialysate flow, and low access recirculation. Although controversial, the preliminary evidence available favor the use of a biocompatible membrane and more frequent or prolonged dialysis to ensure adequate removal of small- and middle molecular weight toxins, yet preventing the loss of essential solutes.

Key words: *Hemodialysis, methods; Hemodialysis, mortality; Risk factors*

Introduction

Since the landmark inception of hemodialysis (HD) for the management of end-stage renal disease (ESRD) in 1960[1], renal replacement therapy (RRT) has entered a new technical era with the introduction of bicarbonate buffer, biocompatible, high-flux membranes, and volumetric ultrafiltration control. Armed with technical advancements and reassured by the definition of adequacy of dialysis by urea kinetics[2,3], short HD had gradually become the accepted practice in the 1980s[4]. Kramer et al.[5] have described the wisdom of shortening the duration of HD when they observed a significantly higher mortality in ESRD patients dialyzed for less than 12 hours weekly. Held et al.[6] have confirmed that patients treated for less than 3.5 hours three times weekly had a twice relative mortality risk compared with patients receiving HD for 4 or more hours. On the other hand, the Centre de Rein Artificial (Tassin, France) report on an unparallelled 69% 10-year survival rate, highest hematocrit values without erythropoietin treatment, and lowest incidence of hypertension without use of antihypertensive drugs, with the old-time method of prolonged slow HD (PHD)[7-9]. However, the catabolic rate of dialysis and indiscriminate depuration of solutes[10-12] have raised concern and uncertainty about the safety and consequences of PHD technique[13].

Kt/V and Risk of Death

Central to the evaluation of the adequacy of short treatment methods is the definition of adequacy, an issue that is still incompletely solved. The National Cooperative Dialysis Study (NCDS)[14-16] has established urea as a valid surrogate marker for uremic toxins and ushered in the era of

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kinetic modeling, but has not defined the standard for optimal dialysis. The statement by Gotch and Sargent[17] from 1985, that a Kt/V of 1.0 represents a dose of dialysis which results in the minimal possible morbidity, and that increasing HD further is "of no apparent clinical value", has since been challenged using data of the NCDS itself[14-16]. Both re-examination of these data and of Gotch's analysis[17], and clinical studies of the relationship of urea removal and ESRD patient outcome[18,19] indicate that the morbidity and mortality rates are improved by dialysis of 1.2 or greater. In a series of 2,311 maintenance HD patients in the USA, Held et al.[20] found the risk of death to decrease progressively as Kt/V was increased to 1.3, but not beyond that rate. Collins et al.[21] also found that the greater the Kt/V, the lower the risk of death. They report that, when a Kt/V greater than 1.0 and lower than 1.2 was taken as a reference, the relative risk of death was 0.67 for Kt/V 1.2 – 1.4, and 0.65 for Kt/V >1.4 in 1,082 non-diabetic ESRD patients. In 691 diabetic HD patients, the relative risk of death was 0.70 for Kt/V 1.2 – 1.4, and 0.59 for Kt/V >1.421. Charra et al.[7] report on a remarkably good survival rate for 445 HD patients treated over the last 20 years. These patients were treated with HD for 24 hours weekly using Kiil dialyzers, and an average Kt/V of 1.67 (survival was 87% at 5 years, 75% at 10 years, 55% at 15 years, and 43% at 20 years)[7]. In 53,867 patients on three times weekly HD in Japan, the Patient Registration Committee of the Japanese Society for Dialysis Therapy (JSDT)[22] report on a progressive decrease in the risk of death as Kt/V was increased to 1.8, however, no further decrease in the risk of death was observed beyond that rate.

The difference in survival on HD among the USA, Europe, Japan and Tassin (France) results may be related to the difference in the dose of dialysis (Kt/V) or in duration of HD sessions. The Tassin group[7] and JSDP[22] have recommended a minimal dose equivalent to a Kt/V of 1.6 and 1.8, respectively, in order to provide a safety limit. Such an approach, combined with a much more effective blood pressure control and appropriate diet, may be the future gold standard for HD therapy.

Dialysis Duration and Risk of Death

Owen et al.[23], in a retrospective analysis of 13,473 HD patients found no association of the risk of death with HD session duration, but did find it with the plasma urea reduction rate (URR) of 65% to 70%, which showed an almost exponential correlation with a Kt/V of 1.3 to 1.6.

Other reports suggest that there is an association between the length of time on HD and risk of death[7,24-26]. The technique, dialysis duration, and clinical outcome of 4 modalities of PHD are well documented in the literature. The patients at the Centre de Rein Artificial currently receive HD with disposable flat-plate or hollow-fiber cellulosic, usually cuprophane, dialyzers with a surface area of 1.1 to 2.2 sqm[7]. Dialysate buffered with acetate (35 mmol/L), generated by a central proportioning system, is delivered at 500 mL/min. Blood access is achieved through arteriovenous fistula in a majority of patients (78%), or by Thomas thigh shunts in some. Patients are dialyzed for 8 hours three times weekly, with a blood flow rate of 200 to 220 mL/min[7]. In Lecce (Italy), patients undergo HD every other day for a minimum of 3 hours to reduce the prolonged 72-hour weekend interdialytic interval[24]. A high level of depuration is targeted and achieved using individualized blood (>300 mL/min) and dialysate (500 to 800 mL/min) flow. Lecce HD has evolved with time and the initial cuprophane membranes (1.2 to 1.6 sqm) have been replaced by more biocompatible and larger (1.4 to 2.2 sqm) synthetic membranes such as polysulfone, polymethylmethacrylate, and AN69. Vascular access is through a distal arteriovenous fistula in all patients[24]. During nocturnal HD practised in Canada[25], the patients dialyse themselves 6 to 7 times weekly for 8 to 10 hours at night[25]. A modified monitor is used to deliver bicarbonate-based dialysate (100 to 200 mL/min) and blood (250 to 300 mL/min) at relatively low rates. In contrast to the Tassin group, a biocompatible polysulfone membrane (0.7 to 1.8 sqm) is used in nocturnal HD. In an attempt to increase the clearance further, the Toronto group has recently resorted to a larger surface area membrane, and increased dialysate and blood flow rates. The vascular access is mostly through Uldall-Cook internal jugular catheters or arteriovenous fistula in some patients. The latest part of the nocturnal HD project is that the patients are monitored remotely from a central station through the Internet[25]. In a different technique, Bouncristiani et al.[26] tried to solve the conflicting need of best depuration without intolerance by increasing the frequency of dialysis to a daily pattern. The patients received ultra-short, low-efficiency bicarbonate HD using a biocompatible polyacrylonitrile membrane with a surface area of 1 sqm. Blood access was achieved through arteriovenous fistula, using an average blood flow rate of 275 mL/min. Most patients dialyzed themselves at home every day for a short duration of 90 to 120 min[26].

Studies have suggested but did not demonstrate an association of longer weekly HD with a lower risk of

death. They have also failed to clarify whether the better patient prognosis was due to longer HD sessions or to the greater dialysis doses. The Kt/V values tend to be high in patients treated with prolonged HD.

Dialysis Duration as an Independent Factor of Death Risk

A potentially important aspect of an optimal HD treatment is the duration of dialysis treatment. Dialysis duration should be long enough to minimize the clinical effects of rapid ultrafiltration, and to provide adequate solute clearance to prevent uremia. Although the choice of dialyzer size, blood flow rate, and dialysate flow rate affects the solute clearance, the most influential prescription parameter affecting the dose of dialysis is dialysis duration. Today we acknowledge that increasing dialysis duration has a beneficial effect on the patient's outcome mostly because of improved removal of small molecular weight solutes. Outcome studies including NCDS[14-16] have failed to support an independent risk of shortened HD time. However, additional considerations that modulate the relationship between dialysis duration and solute removal have recently surfaced.

There are a number of inherent limitations to HD that result in the loss of effective clearance. These limitations cause an inequality between the effective and prescribed clearance, invalidating the assumption that changes in dialysis duration can be compensated solely by proportional modifications in prescribed clearance. Some technical and physiological limitations relate to the fact that blood flow to the dialyse and to various capillary beds is arranged in a set of parallel circuits, and that the body is not a single compartment for urea removal[27,28]. These limitations have important ramifications concerning the HD treatment prescription and its adequacy. In addition, when considering the appropriate duration of dialysis, one must weight those factors that degrade effective clearance so that the compensating increases in the prescribed dialysis treatment duration are adequate. Even when ESRD patients take advantage of current technology, large, high-flux dialyzers, and high blood and dialysate flow rates, a total body Kt/V in excess of 1.0 to 1.2 will require a minimum treatment duration of 4 hours in many HD patients[29]. Unfortunately, without studying cardiac output, cardiopulmonary recirculation, access flow, and access recirculation in each individual patient, it will be impossible to know exactly the time required to lengthen a specific patient's HD session. Only direct quantification of urea removal from the dialysate[30] may eliminate the need of a detailed evaluation of each HD patient's physiology, more accurately define total body effective clearance, and provide a more quantitative basis for the determination of optimal HD treatment duration.

Urea clearance estimated by Kt/V has traditionally been accepted as a yardstick for adequacy of dialysis[31]. The mean Kt/V achieved *per* session by the Tassin group[7] and Toronto group[25] was 1.67±0.41 and 1.0±0.23, respectively. Considering that the Tassin patients were dialyzed 3 times weekly[7], and Toronto patients received 6 or 7 HD sessions weekly, the weekly Kt/V should have been greater with nocturnal HD practised in Toronto[25]. O'Sullivan et al.[32] performed nocturnal HD in a small number of patients with a large surface area (1.8 sqm) polysulfone dialyzer and achieved an astonishing weekly Kt/V of 11.79 to 18.59. The Kt/V delivered weekly is in the range of 2.4 to 3.6 for daily short HD[26] and 4.62±0.76 for Lecce HD[24]. Although the change in urea concentration has been assumed to bear a direct and regular relationship with the concentration of other not clearly identified toxins, it is probably not true. There is increasing evidence that uremic syndrome is more than the accumulation of small, water-soluble, non-protein bound compounds, suggesting a pathogenic role for the denounced middle molecular weight uremic toxins[33,34]. Patients in Tassin received 23.8±2.2 sqm HD weekly (m^2/h/wk)[35] which, when estimated by the dialysis index of Babb et al.[36], yielded 1.53±0.32.37. Similar data are not available for nocturnal HD[25] and daily short HD[26], however, given the high-flux membrane (polysulfone and polyacrylonitrile) used and longer duration of dialysis (8 to 10 hours) in nocturnal HD technique[25], they should be capable of delivering similar or even better clearance of middle weight molecules[37]. Analysis of the Tassin data suggests that a reduction in morbidity and mortality rates may be achieved by an increase in dialysis index[35,36], but not by an increase in Kt/V9, implying that clearance of small and middle molecules may be vital for decreased morbidity and mortality rates[37-39].

In order to determine whether the duration of HD is an independent factor in the risk of death, the JSDT [22,27] attempted to compute the impact of HD session duration on the death risk, which was adjusted by Kt/V, using data of 71,193 HD patients from the 1997 survey. Results of the analysis indicated that even when the higher risk of death, associated with shorter HD session duration, was adjusted for Kt/V, a progressive decrease in the risk of

death was seen as the session duration was prolonged until it reached 5.5 hours[27]. The same analysis also showed that even when the higher risk of death associated with lower Kt/V was adjusted for HD session duration, a progressive decrease in the higher mortality risk was seen as the Kt/V increased until it reached 1.827.

Conclusion

It is not certain whether the effect of reduced dialysis time implies reduction of an already inadequate dialysis dose, or whether there is a mortality risk intrinsic to short time itself, such as increased tendency to hypertension or cardiovascular disease. However, it is certain that the trend to shorter dialysis time has led to underdialysis and adverse clinical effects. Prolonged HD features excellent clearance of small- and middle molecular weight toxins, better control of hypertension and anemia, and better rehabilitation, attesting that it may be closer to the concept of optimal dialysis. There is also a concern regarding the risks of unsupervised home HD and uncertainty about excessive depuration of essential solutes (nutrients, water-soluble vitamins, trace elements), chronic stimulation of the immune system (bioincompatible dialysis materials), prolonged exposure to phthalate, endotoxins, and spallation products from plastic tubing, and increased net protein catabolism[40-42].

Having sifted through available data on dialysis adequacy and dose, and on the role of HD session length, the following conclusions are made: 1) acceptable HD can be delivered in 3 hours or less, but only to small patients or those who have a significant residual renal function; 2) with most of the dialyzers in use, adequate HD cannot be delivered in 3 hours, especially in a setting of less than maximal blood flow and/or high access recirculation; 3) most conventional and even many high-flux and high-efficiency dialyzers are incapable of adequately dialyzing a middle-weight patient in less than 4 hours; and 4) the available evidence favor the use of a biocompatible membrane and more frequent but not very intense HD to ensure adequate removal of small- and middle weight toxins, yet to prevent the loss of essential solutes.

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Sažetak

POVEĆAVA LI KRAĆA HEMODIJALIZA RIZIK OD SMRTI?

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Tehnički napredak omogućio je da bolesnici dobiju veću dozu dijalize u kraćem vremenu. Kada je ispitan odnos između trajanja dijalize i smrtnosti, utvrđeno je da se rizik od smrti značajno povećao usporedno sa skraćivanjem vremena provedenog na dijalizi. Dulja dijaliza i veća učestalost dijalize pozitivno utječu na uklanjanje malih i srednje velikih toksina, omogućavaju ujednačavanje razdiobe otopina između tkiva i krvnih žila, poboljšavaju apetit i dozvoljavaju slobodniju prehranu, a polagana ultrafiltracija omogućava bolju kontrolu hipertenzije. Bolje odstranjivanje uremijskih toksina, normaliziranje staničnog i izvanstaničnog volumena te bolja prehrana smanjuju stopu pobolijevanja i smrtnosti u dijaliziranih bolesnika. Većina danas dostupnih dijalizatora omogućava, u uvjetima maksimalnog protoka krvi i visokog protoka dijalizata, a uz istodobno nizak postotak recirkulacije u krvožilnom pristupu, primjerenu hemodijalizu u trajanju od 4 do 5 sati. Iako neujednačeni, rezultati preliminarnih istraživanja upućuju na to da uporaba biokompatibilnih membrana i češća ili produžena dijaliza omogućavaju primjereno uklanjanje toksina male i srednje velike molekularne veličine, a da pritom ne dolazi do gubitka važnih supstancija.

Ključne riječi: *hemodijaliza, trajanje dijalize, kratka dijaliza, produžena dijaliza, smrtnost*