The never-ending search for the perfect dialysis. Should we move from the best treatment to the best system?

Giorgina B. Piccoli

SS Nefrologia, Department of Clinical and Biological Sciences, Azienda Sanitaria Ospedaliera Universitaria san Luigi, Orbassano, Torino, Italy

Correspondence and offprint requests to: Giorgina B. Piccoli; E-mail: gbpiccoli@yahoo.it

The history of dialysis may be seen as a history of the search for the perfect treatment, combining quantity and quality: ensuring a long life, limiting the impact of the disease and its therapies. Since the start of renal replacement therapy (RRT), each new treatment or schedule has been compared with the previous ones, i.e. peritoneal dialysis (PD) versus haemodialysis (HD), bicarbonate versus acetate, haemodiafiltration versus haemodialysis, long versus short, daily versus intermittent [1–3]. Comparisons have led to context-sensitive, often conflicting results [4,5]. The continuous evolution of treatments has added further confusion. Hence, the search for the perfect dialysis is an unmet goal and a continuous task for the medical community. The paper by Ok et al. [6] is in line with this never-ending quest.

What do we mean by a dialysis treatment, and how do we measure its benefits?

Dialysis should not be defined as a treatment but as a system. It needs supplies: machines, filters, water and regulation of fluxes, electrolytes, ultrafiltration, anticoagulation. It needs a blood or peritoneal access and support therapies. It is built upon a relationship among patients, nurses and physicians, requiring compliance and mutual trust. It requires answers to ethical dilemmas, such as when to start and when to stop treatment, in particular in fragile or incompetent patients [7]. It is a matter of frequency and time, and the final prescription is often the result of compromises involving organization, costs, patients’ and staff’s preferences, clinical needs and compliance [2–5].

Several of these elements have been shown to be significantly related to outcomes. However, no study will have the statistical power to take all of them into account. Theoretically, randomization could at least partly compensate for heterogeneity; however, randomization of the major dialysis treatments (PD versus HD) and of dialysis versus transplantation is clearly unethical, and even randomization of dialysis schedules may be difficult. Indeed, Ok et al., in line with other studies, reported that only a minority of their patients (287 of 1257 patients in 10 centres, 22.8%) was interested in experiencing a long, thrice weekly dialysis schedule [6,8]. Participation in a randomized control trial


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(RCT) was anticipated to be lower, and the authors stated that, in their setting: ‘it was hardly practicable to randomize a patient who was willing to accept prolonged nocturnal haemodialysis because of its previously documented benefits….’ [6]. Thus, while RCTs remain the study designs with the ‘best’ efficacy, nephrologists are facing a dilemma between randomizing a small portion of the dialysis population, often different from the ‘usual’ patients, and designing an observational study. Recently, both choices were undertaken in studies of ‘non-conventional’ dialysis schedules.

The recent trial published in the New England Journal of Medicine, comparing daily versus thrice weekly dialysis, offered an elegant RCT design [9]. However, as underlined in the accompanying editorial, the randomization was troublesome (65 facilities >4 years were needed to enrol 224 patients). In spite of this tremendous effort, the authors stated that ‘it was not feasible to recruit a sample large enough to provide adequate statistical power to assess individual end points of death, cause-specific death…’ [9,10]. The important selection bias was demonstrated by the difference in the yearly death rates in the ‘standard dialysis’ group: 7.5%, versus >18.5% in the overall US dialysis population [9,10].

Ok et al. [6] chose the second policy option, designing an observational study and doing their best to match the control population. Each choice has limits and advantages, and the advantages of the observational study are its closer relationship with the ‘real world’ and a more efficient enrolment rate: 1 year only to enrol 269 patients in 10 facilities [6]. Their study also provided information on the feasibility of nightly dialysis and suggested a flexible organization, in which patients should be free to go back to their previous treatments (~20% would go for a treatment trial, ~25% of them would dropout).

In spite of the design differences, both studies led to similar results, confirming an advantage, for the tested outcomes, of non-conventional schedules. Interestingly, the advantages apply to a subset of relatively young patients (10–15 years younger than the overall dialysis population), probably more prone to choose a more intensive dialysis treatment. The lower baseline mortality may blunt survival differences, but there is quite obvious interest in treatments that are more easily accepted by younger patients, who should attain the ‘best’ survival results.

The paradox of the healthy start of dialysis, of dialysis adequacy, and the interest in ‘non-conventional schedules’

The paradox of prescribing dialysis at about the same glomerular filtration rate (GFR) at which we start RRT may explain why daily and long nightly dialyses are so promising. The controversy between an ‘early’ or ‘late’ start of dialysis is presently settled by a compromise: dialysis should be planned when GFR falls <15 mL/min and may be delayed under strict clinical surveillance [11,12]. Without entering the arena of GFR assessment, we can say that these indications implicitly state that when GFR falls <15–7 mL/min the clinical balance is not granted.

The assessment of dialysis efficiency has likewise been a battlefield in the last 30 years [13,14]. Independently of the formula chosen, if Kt/V is expressed as equivalent renal clearance (EKR), we find that an ‘adequate’ standard thrice weekly dialysis delivers at best 10–15 mL/min of EKR [15–17]. Thus, the standard dialysis dose, delivering an EKR roughly equivalent to the level at which the indications for RRT are set, is probably insufficient to ensure long-term well-being and perhaps long-term survival. Furthermore, a machine-delivered EKR cannot be considered truly equivalent to the renal clearance delivered by the human kidney. Logically, a higher dialysis dose is needed. The question whether the results depend on the schedule or on the delivered dialysis dose is still unanswered, as one does not go without the other; however, it is conceivable that schedule mainly affects tolerance, dose metabolic profile.

The long thrice weekly nightly dialysis ‘Tassin style’, the short daily dialysis ‘Italian style’ and the combination of the two strategies ‘Toronto style’ may allow us to reach an EKR of 20 to >40 mL/min [18–20]. It may be difficult to assess the difference between EKR ranging from 20 to 40 mL/min; however, a simplistic but rather convincing explanation of the superior (or at least equivalent) results obtained thus far by the more intensive dialysis schedules is that an EKR of 20–40 mL/min largely corresponds to a stage in which signs and symptoms of uraemia are usually absent.

The best dialysis? The best patients? Nobody is perfect

Yet, nobody is perfect, and the perfect dialysis does not probably exist. The list of proved or putative side effects of ‘non-conventional treatments’ is probably incomplete, given the limited worldwide experience, mainly gathered in selected enthusiastic centres and in selected. A detailed analysis goes beyond the scope and space of the present discussion; however, two main clinical concerns and the cost issue should be mentioned.

The first ones are related the vascular access, as the fistula may be challenged by more frequent venipunctures (in daily dialysis) or by prolonged lodging of the needles (in nightly dialysis); the choice of an indwelling catheter may be alternative in selected cases but has to be balanced against the well-known infectious risks [8–10]. The second regards the iatrogenicity of dialysis: highly efficient dialysis may deplete the body of small molecules or trace elements, as it has been demonstrated for phosphates, and the contact with non-ultrapure water may elicit inflammation. The good survival results so far obtained are reassuring, at least in the medium run; further research is highly needed [8–10].

The cost issue is complex and context dependent. In the western world, the supplies are presently accounting for a minor proportion of the dialysis costs. Thus, increasing the frequency affects the costs depending upon the organization
(for example, in-hospital daily dialysis, more sessions on the same machine, with the same nurses, development of self-care or home treatments; assessment of standards of care in ‘soft’ long in-hospital nightly dialysis). One size does not clearly fit all, and the novel requirements may give a strong input for economical and organizational analysis.

The question on the ‘best’ patients is strictly linked to the previous issues. The only requisite is probably, at present, a well functioning vascular access. In fact, the reported advantages are both for the young (better metabolic balance and improvement in survival) and for the frail elderly (higher tolerance, metabolic control). At least in the (possibly biased) opinion of the writer, the choice should be up to the patients, who are the only ones able to balance, after a trial of treatment and discussion with the caregivers, the logistical constrains in their daily life versus the perceived or documented clinical advantages.

No man is an island. Dialysis is not an island

Dialysis is not an island; it is a mirror of the society, of the global care and of the sequential alternatives in CKD: ‘predialysis’ and transplantation. Early referral not only improves survival but also increases the chances of self-care dialysis, recognized as a therapy in itself [21–23].

The availability of kidney transplantation and the prevalence of young patients on dialysis show an inverse relationship. Baseline life expectancy differs according to age, and the risk of death increases non-linearly with the ‘vintage’ on RRT. Consequently, the baseline characteristics of the dialysis population affect the results of the comparisons between treatments.

Dialysis is expensive; RRT consumes ~2–5% of the health care budget in countries where dialysis is available without restrictions [24]. Thus, the ‘standard’ schedule (4 h, 3 times per week), initially pursued in the search for a treatment efficient enough to ensure survival but also fit to treat more patients with the same limited resources, became a pragmatic compromise between the ‘best’ treatment and the organizational needs of the dialysis wards [25,26]. Cambi [26] concluded his pivotal paper entitled ‘Short dialysis schedules, finally ready to become a routine?’ by saying that the ‘continuously growing number of patients obliged us to select very few and very reproducible clinical parameters’ ... ‘in 1971, with 12 nurses, we were performing 254 dialyses per month. In 1974, with 12 nurses, we were performing 750...’. The need to limit the ‘caregiver doses’ to contain costs was a formidable push towards standardization of dialysis, with a preference for large ‘industrialized’ facilities over smaller flexible units. Flexibility remained limited to a few treatments, above all home haemodialysis.

Is home haemodialysis an answer?

The fortunes of home haemodialysis reflect different driving forces: a life-saving treatment in the 1960s and ‘70s, it started to decline in the ‘80s, as the growing number of facilities allowed not only hospital treatment for everyone but also permitted reduced travelling times, without the need to involve a family caregiver in a society in which the number of working couples was increasing [27,28]. The dream of transplantation as a life-long solution for young patients, the rising tide of elderly patients, and, in several settings, the low reimbursement for home haemodialysis limited the interest among the medical community.

In the new millennium, however, home haemodialysis is being rediscovered, thanks to social changes and clinical issues [29]. At present, the empowerment of patients and the economic crisis, with the loss of jobs and the need to preserve a full-time working activity, play a role in the revival of home treatments, especially when coupled with incentives for caregivers. Home treatments cost less, and in the present global crisis, this is a tremendous incentive for home-based therapies. In this regard, dialysis may follow new organizational solutions designed for heart failure or cancer therapy [30].

Home dialysis has a further advantage: it ensures flexibility, allowing increased time or frequency at low costs, delivering a higher dialysis dose. While the thrice weekly nightly hospital dialysis is a suitable solution for some patients, long and frequent treatments are best performed in patients’ homes, and nightly treatments for 6–7 days per week are only compatible with home care. Although ‘non-conventional’ dialysis schedules are not (and should not) be limited to home haemodialysis, the disturbance to our rigid, conventional, expensive hospital organization caused by the addition of new options is limited by the increase of home dialysis.

Hypothesis: survival in a multiple-choice dialysis system

After almost five decades of comparisons between treatments, in the search of the ‘best’ dialysis modality, we might wonder what would happen if patients could really choose the dialysis modality best suited to their needs (clinical well-being, social life and work) and if they would easily switch among treatments in the case of side effects or personal preferences. Presumably, the advantages and disadvantages of each technique would be redistributed in the system, like molecules moving through a semipermeable membrane. Thus, the addition of a new successful treatment would result in a global improvement; in this context, the equivalence between the ‘best’ and ‘worse’ treatments would prove the global performance of the system (Figure 1).

If this hypothesis is true, the best results would be recorded in multiple-choice dialysis systems and would be improved by adding further options.

Indeed, one might wonder whether a multiple-choice system is financially bearable. It is difficult to say; however, when physicians choose a treatment, they try to choose the best one. Thus, a skilled physician and an experienced patient should make the same choice. What physicians may not be able to readily identify is the impact on daily life. Thus, we might assume that patients are more capable in identifying the best compromise between
well-being and daily life, at the best by ‘trial and error’, experiencing different treatments. If this holds truth, and if physicians and patients have free access to the best treatments, a flexible system should require a dynamic clinical and organizational approach, but should not increase the costs. In an ‘ideal’ world of wise physicians and empowered patients, the empirically tried ‘system’ and the prescribed ‘treatment’ became equivalent.

While only study designs comparing different dialysis systems can verify this hypothesis, we can advocate a revival of home haemodialysis, to date the best option allowing a tailor-made dialysis, with the requisite of empowerment of patients and caregivers.

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(See related article by Ok et al. Comparison of 4- and 8-h dialysis sessions in thrice-weekly in-center haemodialysis. Nephrol Dial Transplant 2011; 26: 1287–1296)

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Fig. 1. In the usual ‘rigid’ systems, the patients start with a treatment and switch to a different one only in the case of severe clinical problems (for example fistula problems on daily dialysis or extreme low tolerance on standard treatment). Thus, it is relatively easy to individuate the features of each treatment or to compare them, at best with an intention to treat schema. In a flexible system, the patients are left ‘free’ to experience different dialysis treatments and are encouraged to change treatment in the case of minor side effects, hypothetically linked to the treatment. Thus, at the end of the study period, the effects of treatments are entangled and the dialysis system has to be analysed as a whole. In this context, the addition of a single effective treatment should improve the performance of the whole system.

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