Less water for haemodialysis: is multiple pass the future pace to go?

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Introduction

Tentori et al. investigated the influence of dialysis treatment time (TT) on the intermediate outcomes and survival in patients on in-centre three times weekly haemodialysis [1]. Data were used from the international Dialysis Outcomes and Practice Patterns Study (DOPPS), which is a prospective cohort study. The study by Tentori et al. included 37 414 in-centre haemodialysis patients from seven countries (France, Germany, Italy, Japan, Spain, the UK and the USA) in DOPPS 1 (1996–2001), and from these and an additional five countries (Australia, Belgium, Canada, New Zealand and Sweden) in DOPPS 2 (2002–04) and DOPPS 3 (2005–08) [1]. Patients were dialysed thrice-weekly with a prescribed TT of 120–420 min, and detailed case-mix and comorbidity data were collected at study enrolment. TT was analysed as a continuous variable (per 30 min longer TT) and as a categorical variable (<210, 210–240 and >240 min). Mortality was defined as all-cause mortality, cardiovascular death and sudden death. The mean follow-up was 19 months, during which 8961 patients died (mortality rate: 0.15 per year). In their analysis, Tentori et al. applied both a patient-based and an instrumental variable approach using the dialysis facility as an instrument to reduce the bias as introduced by unmeasured confounders [1].

The main findings of this study are first, longer TT was associated with lower mortality in Japan, Europe and Australia/New Zealand, but not in the USA or Canada; second, TT was strongly associated with sudden death, even after adjustment for patient comorbidities such as diabetes and atrial fibrillation, which are risk factors for sudden death; third, longer TT was associated with better anaemia, phosphorus and blood pressure control, which might be an indication of a possible mechanism for improved clinical outcomes; and fourth, within each geographical region, no interaction was found between TT and dialyser blood flow rate, or between TT and Kt/Varea.

Impact of treatment time on solute removal

Different studies already described the increased solute removal during prolonged dialysis. The removal of middle molecules, like β2-microglobulin, was found significantly increased (40–80%) when prolonging dialysis from 4 up to 8 h, even when maintaining the same volumes of processed blood and dialysate [2, 3]. The advantage of prolonged dialysis for β2M removal mainly finds its origin in the strong retarded intradialytic solute transport from the extraplasmatic compartment into the plasma [4, 5]. Also the rather limited clearance in the dialyser plays an important role in transport retardation, as indicated by Leypoldt [6] showing a direct association between time-averaged β2M concentrations and the product of clearance times weekly TT.

The removal of small and water-soluble solutes is also enhanced with prolonged dialysis, especially for solutes that are more sequestered, like phosphate. Herewith, retardation of phosphate transport in the patient can be modelled by either a four-compartment model [7] or an infinite inaccessible compartment with a constant concentration [8, 9]. Prolonging dialysis from 4 to 8 h decreases pre-dialysis phosphate levels by 6.5% [6], and increases phosphate removal by 27–49% [2, 3]. Guanidino compounds like creatinine and methylguanidine, which are distributed in a volume larger than that of urea, were found to have most benefit from a prolonged dialysis strategy [10]. Even for urea, which is transported easily through the cell membrane [11] and is distributed in a rather limited volume (around 55% of total body weight), removal significantly increases (22–26%) with protracted dialysis [2, 3], although Kt/Varea was not different, as also found by Tentori et al. [1]. This seemingly contradictory finding can be explained by a smaller post-dialysis rebound in the case of long dialysis. Hence, this aspect makes Kt/Varea not a good parameter for dialysis adequacy, especially not for short and intense dialyses.

Impact of TT on outcome

Tentori et al. found that longer TT is associated with better control of anaemia, phosphorus levels and blood
pressure [1]. Different studies dealing with prolonged dialysis already reported about a lower need for erythropoiesis-stimulating agents [12–14], lower pre-dialysis phosphorus levels [6,12] and better blood pressure control [12, 15–18]. The latter might be due to the decreased progression in arterial stiffness in patients on prolonged dialysis [19]. All these factors might play an important role in the lower cardiovascular morbidity and mortality [14, 20], and the better overall survival [21].

Discrepancies between the impact of TT among countries

The present study found that longer TT was associated with lower mortality in Japan, Europe and Australia/New Zealand, but not in North America (USA and Canada). How can this discrepancy be explained? TT prescription varied significantly across countries, with the longest TT in Australia/New Zealand (255 ± 41 min) and the shortest TT in the USA (212 ± 32 min). Table 1 shows an overview of the percentage of patients per TT category within a geographical DOPPS region (as derived from Table 1 in Tentori et al. [1]). For North America, only 6% of the patients were treated longer than 240 min, which makes it rather difficult to investigate the impact of prolonged dialysis without losing statistical power. However, the mortality data in Japan, Europe and Australia/New Zealand, as published by Tentori et al., clearly confirm the previously reported survival benefit when performing longer dialysis. Hence, prolonged dialysis should be considered as a way to significantly improve dialysis patient outcome.

Other factors influencing mortality and differing among countries

In 1990, Held et al. [22] published the 5-year survival of all end-stage renal disease patients from the USA, Europe and Japan, showing a much worse survival rate in the USA compared with Europe, and an even larger difference if compared with Japan. Since these data were based on regional registries, the first question raised was about the data quality. As an answer to this question, the Dialysis Outcomes and Practice Pattern Study (DOPPS) was initiated in 1996. However, data from DOPPS 1 (1996–2001) confirmed Held’s findings, even after adjustment for several characteristics and comorbidities [23]. Also recently, based on registry data, Kerr [24] confirmed the 5-year survival in haemodialysis patients to be the worst in the USA. In the same study, differences in dialysis strategy were investigated in order to explain the discrepancy in mortality among geographical regions. Several differences were found between the USA and Europe, as discussed hereafter.

A first difference between the USA and Europe is the delivered dialysis dose, i.e. Kt/Vdrea. However, the HEMO study did not find any better survival by increasing Kt/Vdrea from 1.32 to 1.71 [25]. It should be noted that in the latter study, the increase in dose was mainly accomplished by increasing dialyzer clearance, while TTs were 190 versus 219 min. in the low and high Kt/V group, suggesting that TT was not distinctive enough to have an impact on mortality: if in the HEMO study, patients would have been randomized to higher Kt/V to be achieved by increasing ‘t’ rather than ‘k’, perhaps a more positive outcome would have been obtained.

A second difference among countries is the use of high-flux dialyser membranes, which is more prevalent in the USA compared with Europe [24]. However, the US HEMO study did not find a better survival when using high-flux membranes, although there was a better survival when using membranes of smaller pore size than those currently used in Europe such as high flux [25]. The recent European MPO (Membrane Permeability Outcome) study found a significant benefit in survival among the patients with a serum albumin level lower than 4 g/dL [26], which composes the majority of today’s haemodialysis patients.

The vascular access type is the third difference among the two regions, with a 48, 23 and 29% use of fistula, graft and catheters, respectively, in the USA, while these proportions are 70, 10 and 20% in Europe [24]. A previous DOPPS study by Pisoni et al. [27] showed that mortality was most influenced by model adjustment for vascular access type, while adjustment for TT showed a more limited impact. This implies that vascular access might play an even more important role in patient outcome.

A fourth difference in dialysis practice is the application of haemo(dia)filtration, currently used in Europe for 30–40%, while rarely if ever applied in the USA due to FDA regulations. Haemodiafiltration has been associated with better removal [28, 29] and better survival in an observational study [30] as well as in a small controlled trial [31]. In spite of better survival in the latter study, again, no differences in applied Kt/Vdrea were seen.

Hence, besides the vascular access choice, prolonging dialysis seems to be the most rewarding approach to enhancing solute removal and patient survival.

Alternative dialysis strategies improving dialysis outcome

Besides prolonged dialysis, frequent dialysis is also found to have benefits, by decreasing pre-dialysis concentration of protein-bound compounds [32] and advanced glycation end-products [33], by increasing the removal of guanidino compounds with a small distribution volume [10] and by offering a better control of hyperphosphataemia [34]. More frequent dialysis enhanced survival in a matched control study [35], and in a recent randomized controlled trial over a 12-month follow-up period, six times weekly was superior for a composite primary endpoint of death or

Table 1. Percentage of patients per TT category within a DOPPS region

<table>
<thead>
<tr>
<th>TT category</th>
<th>North America</th>
<th>Europe/ANZ</th>
<th>Japan</th>
</tr>
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<tbody>
<tr>
<td>&lt;210 min (%)</td>
<td>32</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>210&lt;TT&lt;240 min (%)</td>
<td>62</td>
<td>63</td>
<td>70</td>
</tr>
<tr>
<td>&gt;240 min (%)</td>
<td>6</td>
<td>20</td>
<td>16</td>
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a decrease in the RAND-36 physical-health composite score, and change in left ventricular mass, and was also associated with improved hypertension control [34].

The problem with these strategies, deviating from standard three times per week dialysis, is that there is a tight restraint upon dialysis times when they are to be applied in centre. Home haemodialysis, prolonged overnight dialysis or self-care dialysis can offer more flexibility for the patient, and simultaneously more adequate dialysis, making these options a valid alternative to classical in centre dialysis. However, there are also several restraints to these approaches, including a need for an acceptable physical condition, willingness of the patient to perform such a strategy and insufficient reimbursement in many countries not covering the increased need of electricity and water imposed by these alternative strategies [36].

Conclusion

The article by Tentori et al. confirms previous findings about the positive impact of TT on outcome, such that there should be an incentive to perform longer dialysis sessions [1]. Furthermore, taking into account that urea kinetics is not very representative for the kinetics of other solutes, including small and water-soluble solutes, we think that the usual marker for dialysis adequacy, Kt/V urea, is a poor marker for many alternative timeframes, such as frequent and extended dialysis. Hence, the main challenge nowadays is to characterise a better marker reflecting dialysis adequacy and/or outcome.

Conflict of interest statement. None declared.

(See related article by Tentori et al. Longer dialysis session length is associated with better intermediate outcomes and survival among patients on in-center three times per week hemodialysis: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). Nephrol Dial Transplant 2012; 27: 4180–4188.)

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Twist: a new player in the epithelial–mesenchymal transition of the peritoneal mesothelial cells

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Abstract

Background. The peritoneal membrane is a vital structure for peritoneal dialysis (PD) patients. It has been increasingly recognized that the transition of the peritoneal lining mesothelial cells into a more fibroblastic phenotype is a key step in peritoneal membrane injury.

Methods. Relevant literature was reviewed and summarized.

Results. Epithelial-to-mesenchymal transition (EMT) is a basic cellular process that occurs in a variety of physiologic and pathologic processes. The hallmark of this process is a loss of epithelial markers, and E-cadherin is a prototypical epithelial transmembrane protein. E-cadherin expression is suppressed at many levels and the gene is regulated by a family of transcription factors. Twist is one of the lesser studied E-cadherin regulatory factors, which belongs to a larger family of basic helix-loop-helix DNA-binding proteins. In this issue of Nephrology Dialysis Transplantation, Cuixiang Li reports on experiments where the expression of Twist led to a decreased expression of E-cadherin and the evidence of EMT. In an in vitro model of dialysate exposure, Li demonstrates that Twist expression is increased in the injured peritoneal tissues.

Conclusions. These important observations are the first to link Twist to mesothelial EMT and peritoneal membrane injury. Like most novel observations, this paper leaves many questions unanswered. Twist is only one of several transcription factors involved in EMT and how these factors interact will require further investigations. Furthermore, the question of whether Twist interacts at multiple levels in the EMT process, or simply gives an initial push to the process, is left unanswered. Finally, to bring these early significant findings to the bedside as potential therapies for PD patients will require further innovation.

Keywords: epithelial–mesenchymal transition; matrix metalloproteinase; peritoneal fibrosis; snail; Twist

The peritoneal membrane is a seemingly simple structure, which provides life support for patients with renal failure who rely on peritoneal dialysis (PD) as their renal replacement therapy. Over time, most PD patients develop fibrosis and angiogenesis of the peritoneal tissues which impacts negatively on the functional characteristics of this membrane. An emerging concept in organ fibrosis suggests that the cellular protagonist—the myofibroblast—can be derived from the transition of injured epithelial cells. This epithelial-to-mesenchymal transition (EMT) has been observed in animal models of peritoneal injury [1] and in the peritoneal tissue of patients on PD [2].

EMT is a cellular program consisting of a loss of cell–cell and cell–matrix interaction; loss of cellular polarity; cytoskeletal rearrangement with an increased expression of α-smooth muscle actin (α-SMA) and basement membrane degradation with subsequent migration or invasion. In a recent review article, Kalluri and Weinberg [3] suggested that EMT occurs in different settings. Type 1 EMT is an essential process in development. Type 2 EMT is the phenomenon we are interested in and describes a beneficial event in normal wound healing or pathologic event in fibrosis. Type 3 EMT occurs in the setting of metastatic transformation of cancer cells.