Comparison of characteristics of centres practising Incremental and Conventional approaches to Haemodialysis Delivery and post-dialysis recovery times and patient survival

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Abstract

Introduction
Conventional haemodialysis (HD) involves treatment times of around 4 hours thrice weekly, taking no account of residual kidney function (RKF). In Incremental HD the frequency and duration of dialysis sessions are individualised according to RKF. There are no studies comparing these approaches. We utilised data from a recent multicentre study to compare patient characteristics and outcomes between a centre practising incremental HD and others using a conventional approach.

Methods
709 patients attending for routine outpatient HD in five UK centres were studied. One centre practiced incremental dialysis (n = 254) and four conventional HD (n = 455). Data collected included demographics, comorbidity, dialysis parameters, routine biochemistry and haematology, recovery time post-dialysis, and Beck depression inventory-II score (BDI-II). Patients were followed for a minimum of 12 months.

Findings
Pre- and post-dialysis BP, serum calcium and phosphate were higher in the Incremental centre, whilst sessional Kt/Vurea was lower (all $p < 0.001$), as was the proportion of patients with a mean post-dialysis BP <100 mmHg ($p = 0.011$). Patients recovered from their HD session more quickly in the Incremental centre, with significantly more patients reporting recovery within one and four hours Short-term survival was significantly better in the Incremental centre both unadjusted and adjusted for age, gender, ethnicity, dialysis vintage, anuria, history of cancer, heart disease, diabetes mellitus, body mass index, serum albumin, BDI-II score, and sessional Kt/V.

Discussion
The association between incremental dialysis, shorter post-dialysis recovery times and improved short-term survival may be related to reduced haemodynamic stress as a consequence of less intensive ultrafiltration and reduced length of dialysis sessions. Prospective studies are required to test this hypothesis.

Introduction

The most common approach to haemodialysis (HD) delivery in the UK involves the prescription of thrice weekly HD with sessional dialysis times of 3.5 to 4 hours [1]. This conventional approach takes no account of the amount of residual kidney function (RKF) that individual patients may retain. This approach also usually involves the practice of probing for dry weight at dialysis initiation which, if aggressively deployed, may result in rapid loss of RKF [2].

Recently more individualised approaches to dialysis prescription have begun to be advocated [3]. Studies have described more intensive treatments which involve increased sessional duration or frequency which may be carried out during the day or nocturnally and in centre or at home. Benefits on patient survival and aspects of quality of life have been described, particularly for home HD patients [4], although not universally [5]. There are also reports of an incremental approach to dialysis delivery [6]. In this approach the frequency and duration of dialysis sessions are individualised to take account of RKF. This is achieved by aiming to exceed the same minimum target levels of small solute clearance as deployed in conventional treatments, though in the incremental setting the target is a composite of dialyser and native kidney clearances. The amount of dialysis to be delivered can be estimated from measuring residual renal function from urinary urea clearance [7], and is then successively increased as RKF is lost [8]. This approach entails the regular measurement of RKF and pragmatic efforts to preserve it, such as avoidance of dialysis-related hypotension.The practice of incremental initiation of haemodialysis varies between countries [9,10]. There have been number of observational studies comparing the effect of twice-weekly initiation of HD on the retention of residual kidney function and on survival [9-12], with reports of reduced, similar and better survival compared to patients initiating dialysis with the standard paradigm. However, there have been very few studies comparing patient reported outcomes of incremental and conventional approaches to dialysis [12]. Health related quality of life (HRQOL) is markedly reduced in HD patients compared to the general population, and patient focus groups have reported that patients are more

concerned about their quality of life than actual survival [13]. In this paper we have utilised data collected during a recent multicentre study [14], to compare parameters between one of the centres practising incremental HD and four others which utilised a conventional approach.

Methods and Patients

Patients

Patients attending for routine outpatient HD in five UK dialysis centres were recruited into a screening trial for depression. Patients over the age of 18 years old who had been receiving haemodialysis for more than 3 months were eligible for inclusion. Patients who could not read and speak English and those with cognitive impairment were excluded [15].

Dialysis Practices

All patients dialysed with high-flux haemodialysers and all five centres prescribed dialysis sessions to achieve UK Renal Association standard sessional Kt/Vurea target [16]. One centre practiced incremental dialysis, reducing dialysis session length taking into account residual renal function [17]. In four of the centres, including the incremental centre, the majority of patients received haemodialfiltration (HDF) [18]. Patients were reviewed in centres monthly, and post-dialysis target weights adjusted according to the supervising nephrologist. Decisions on changing target weight were based on clinical examination of peripheral oedema, jugular venous pulse, lung auscultation, and review of intra-dialytic hypotensive episodes [19]. Three centres, including the incremental centre, had access to bioimpedance [20], and one centre regularly used blood volume monitoring [21]. Whereas all five centres reviewed post-dialysis blood pressures, there was a difference in interpretation of pre-dialysis blood pressures, with the incremental centre not taking these into account when determining target weight. Three of the centres, including the incremental centre requested urine collections from patients and prescribed diuretics to patients passing urine.

Data Collection

Demographic data including age, gender, self-report ethnicity and residential status, and dialysis vintage (months since dialysis initiation) was obtained from computerised hospital medical records. Comorbidity including the presence of diabetes and heart disease was collected using a validated patient questionnaire [22] along with patient self-reported depression using the Beck Depression Index-II (BDI-II), and self-reported anuria ("do you pass more than one cupful of urine daily – yes/no").

In addition, the following data was collected in relation to a single HD session: target weight, sessional KtVurea, pre- and post-HD sessional blood pressures, and episodes of intra-dialytic hypotension, defined as a fall in systolic blood pressure (SBP) ≥20 mmHg, and self-reported time taken to recover post-dialysis - categorised into the following time intervals < 1 hour, 1-4 hours, 4-8 hours, 8-12 hours, and >12 hours. Routine biochemical and haematological data from routine monthly investigations were obtained from computerized hospital records closest to the day of the dialysis session.

Follow-up

Patients were followed up for a minimum 12 months after completion of questionnaires. Date of death, transplantation, and transfer to other centres during follow-up were recorded.

Ethics

All patients provided appropriate informed consent in keeping with the Helsinki agreement, prior to receiving questionnaires. The study received ethical approval (National Research Ethics Service Committee London - Bentham, reference 12/LO/1554), and was registered (ISRCTN06146268).

Statistical analysis

Data was checked for normality using the D'Agostino and Pearson method, and is reported as mean and standard deviation, or median and interquartile range, or

percentage. Intergroup analysis was by t test or Mann Whitney U test, or Chi square analysis with correction for repeated tests and for small numbers, where appropriate. Multivariate logistic analysis was used for determinants of time to recover post haemodialysis including variables significant on univariate analysis, and those which differed between centres. Variables were then excluded if not significant or did not improve model fit in a step backward approach, and models were checked for collinearity. Cox proportional models were used for survival analysis. Analyses were performed with Graph Pad Prism (Graph Pad Prism Version 7.0, San Diego, USA) and SPSS 24 (SPSS, IBM Corporation, Armonk, New York, USA). Statistical significance was taken as $p<0.05$.

Results

Seven hundred and nine patients were recruited, 254 in the centre practising incremental HD and 455 in the four centres practicing conventional HD (Table 1). There were no differences between the incremental and conventional centres with respect to age, gender, the presence of anuria, heart disease, diabetes, cancer and previous transplantation, target weight, haemogobin concentrations, serum albumin, and self-reported BDI-II depression screening questionnaire. However, there were a number of differences between the centres. A higher proportion of patients in the incremental centre were of white ethnicity ($p < 0.001$). Pre- and post-dialysis blood pressures were also higher in the incremental centre (all $p < 0.001$). The prevalence of a fall in systolic BP> 20mm Hg was similar in both groups but the proportion of patients with a mean post-dialysis blood pressure <100 mm Hg was lower in the incremental centre ($p = 0.011$). In addition, sessional Kt/V was lower in the incremental centre ($p < 0.001$), whilst both serum calcium and phosphate were significantly higher (both $p < 0.001$).

Post-Dialysis Recovery Time

Seven hundred and one (98.9%) patients completed the time to recover post-HD questionnaire. Just under a quarter of patients (24%) reported that they had recovered from dialysis within one hour, 51% within 4 hours, 66% within 8 hours, 77% within 12 hours, but 23% took more than 12 hours to fully recover. Patients reported recovery from a HD session more quickly in the incremental centre (Table I and Figure 1). The differences were significant at one and four hours. Other significant univariate associations of recovery time are summarized in Table 2. In general, greater age, male gender, lower body mass index (BMI), the absence of anuria, living with a partner rather than alone, and lower BDI-II scores, as well as incremental HD, were associated with more rapid recovery times. Whereas a post-dialysis systolic pressure < 100 mm Hg was associated with delayed recovery > one hour. In logistic regression models incremental HD was a significant independent predictor of post-dialysis recovery time < 4 hours (Table 3), when corrected for age, gender, ethnicity, anuria, dialysis vintage, target weight, BDI-II score, heart disease, diabetes, post-dialysis systolic BP < 100 mm

Hg, sessional Kt/Vurea, although the model explained only 9% of the variation in recovery times in this period.

Survival

Short-term survival was significantly better in the incremental HD centre that in the conventional HD centres in both unadjusted and adjusted analyses. Figure 2A depicts the output of a Kaplan-Meier analysis suggesting a significant survival benefit for patients in the incremental centre ($p = 0.04$). Table 4 and Figure 2B depict the findings of a Cox model of incremental dialysis practice on survival. Variable included in the model were age, gender, ethnicity, dialysis vintage, anuria, history of cancer, heart disease, diabetes mellitus, body mass index, serum albumin, BDI-II score, and dialysis sessional Kt/Vurea and incremental HD centre. In this model dialysing in the incremental HD centre was a significant independent predictor for a reduction in the risk of mortality. Those dialysing in the centre practising incremental HD had a 38% reduced mortality risk compared to those dialysing in the conventional HD centres.

Discussion

Incremental HD was associated with reduced post-dialysis recovery times and improved short-term survival compared with conventional HD in spite of less intense treatment, as evidenced by lower sessional Kt/Vurea, higher pre- and post-dialysis blood pressures and poorer control of phosphate levels. It is therefore likely that the effect on recovery times is secondary to reduced haemodynamic stress as a consequence of the combination of less intensive ultrafiltration and reduced length of dialysis sessions. Taking account of RKF in dialysis prescription may underlie both these factors. Previous reports have observed that dialysis centres allowing higher pre-dialysis blood pressures have been reported to have a lower incidence of symptomatic intra-dialytic hypotension [23]. As well as an incremental approach, more rapid recovery times were associated with less hypotension post dialysis, as fewer patients had post-dialysis systolic pressures of <100 mmHg, preserved RKF with fewer patients reporting anuria and also those with lower BMI. Previous studies have shown that patients with higher body weights tend to have a higher prevalence of volume depletion pre-and post-dialysis [24], and this may be due to the reduced water content of fat tissue compared to muscle [25]. Female patients reported longer recovery times, and previous studies have reported that female dialysis patients re more likely to suffer with intra-dialytic hypotension [26]. All these factors are in keeping with a haemodynamic explanation for the differences in recovery times reported between incremental and conventional centres and is in keeping with short recovery times reported from other studies reporting haemodynamically stability [27].

Clearly though this is not the only potential explanation for post-dialysis recovery times. There was a major association with distress as evidenced by the strong association with symptoms of self-reported depression. The BDI-II questionnaire contains a number of questions related to fatigue [28], and fatigue is commonly reported by dialysis patients [29], and this overlap may well account for the difference between the higher prevalence of self-reported depression using screening questionnaires such as the BDI-II and the much lower prevalence reported when

patients are formally reviewed by psychiatrists [14]. It is likely that differences in dialysis treatments may affect early recovery, whereas longer recovery times patients reflect general fatigue [30].

Haemodynamic factors may also play a major role in the differences in short term survival we have described. Ultrafiltration during HD may result in reduced organ perfusion during which may have detrimental consequences such as reduced blood to the heart leading to cardiac stunning [31], and to the brain [32] which may increase cognitive decline [33], and post-dialysis hypotension which is reported to reduce patient survival [34].

However, the more conservative approach to ultrafiltration, given the higher peri-dialytic blood pressures in the incremental centre may expose patients to the adverse effects of increased systemic blood pressure. Despite increased pre- and post-dialysis blood pressures, patients dialysing with the incremental approach had better short-term survival, despite having a lower proportion of patients from the ethnic minorities, who have greater survival than white patients in the UK [35]. What constitutes optimal blood pressure control in HD patients remains to be established [36]. Blood pressure varies not only throughout the HD cycle and with fluid accumulation, but there is also a significant white coat effect in the pre-dialysis period making routine pre-dialysis blood pressure difficult to interpret [36,37]. Cardiovascular comorbidity is common in HD patients and further complicates interpretation of blood pressure targets. Extrapolating targets from the general population is unlikely to be helpful and may be harmful [23], as evidenced by a recent pilot trial designed to achieve lower blood pressures in dialysis patients which reported increased intra-dialytic hypotensive episodes in patients randomised to achieve lower blood pressure targets [38]. As such it is likely that an individualized approach is required.

There are many limitations to our observational study including its retrospective nature and the likelihood of other unaccounted potential differences between the study centres which may contribute to the differences reported, despite dialysis centres following common clinical guidelines [16].

However, our findings may give an indication the more aggressive dialysis treatments may impact on both patient experience and outcomes and suggest the need for further prospective study of incremental dialysis in patients initiating dialysis.

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Figure 1. Percentage of patients reporting post-dialysis recovery times at < 1 hour, < 4hours, <8 hours, and <12 hours in patients dialyzing in a centre practicing incremental dialysis and those using standard dialysis schedules.

Figure 2. A. Unadjusted patient survival in patients dialyzing in a centre practicing incremental dialysis and those using standard dialysis schedules

B. Patient survival adjusted for age, gender, ethnicity, dialysis vintage, anuria, history of cancer, heart disease, diabetes mellitus, body mass index, serum albumin, BDI-II score, and dialysis sessional Kt/Vurea in in a centre practicing incremental dialysis and those using standard dialysis schedules.