Effect of change in renal replacement therapy modality on laboratory variables: a cohort study from the UK Renal Registry

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Abstract

Background. Although previous comparisons have shown differences in biochemical and haematological variables between patients on haemodialysis and peritoneal dialysis and those with functioning transplants, these could be due to case mix rather than being due to differences in the types of renal replacement therapy (RRT). The longitudinal follow-up of individual patients after the change in modality has not hitherto been described.

Methods. From the UK Renal Registry (UKRR) database of patients receiving RRT between 1 January 1997 and 31 December 2004, we identified two cohorts: 2033 patients who had been on either haemodialysis (HD) or peritoneal dialysis (PD) for at least a year and who subsequently underwent transplantation and then survived at least a year (PD+HD to TP); and 892 patients who had been on PD for at least a year who changed to HD and then survived at least a year (PD to HD). In both cohorts, the following variables were studied for the four quarters before and after the change of modality: blood haemoglobin and serum, ferritin, albumin, bicarbonate, cholesterol, calcium, phosphate and parathyroid hormone (PTH) concentrations. No information on drug treatment was available.

Results. In the PD+HD to TP cohort, transplantation was associated with a rise in haemoglobin, albumin and bicarbonate, a fall in ferritin and phosphate, no change in calcium, a fall (but not to normal) in PTH and a transient rise in cholesterol concentrations. In the PD to HD group, the change in modality was associated with a significant temporary fall in haemoglobin, a progressive rise in ferritin, albumin, phosphate and PTH, no change in calcium and fall in bicarbonate and cholesterol concentrations.

Conclusion. The change from HD to PD is associated with a significant fall in the haemoglobin concentration; anticipation of this change might enable clinicians to ameliorate it. Persistent hyperparathyroidism is common after kidney transplantation.

Keywords: haemodialysis; kidney transplantation; laboratory variables; modality change; peritoneal dialysis

Introduction

In the UK, as in most other developed countries, most adult patients (96%) commence renal replacement therapy (RRT) on dialysis rather than with a transplant. Although the use of peritoneal dialysis (PD) is decreasing in the UK [1], it still accounts for 25% of patients starting RRT. The UK Renal Registry (UKRR) has consistently reported differences between dialysis modalities in the achievements of audit measures for laboratory variables [2,3], e.g. lower serum phosphate concentration in PD compared to haemodialysis (HD) patients. However, it is unknown whether this is due to differences in the types of patients treated with different modalities, or due to intrinsic differences in the results achieved with the different treatment modalities. The use of observational data from registries that collect data on all patients, rather than selected subgroups or patients selected for participation in clinical studies (e.g. randomized controlled trials), provides the best opportunity for describing outcomes in routine clinical practice. The UKRR's ability to collect, validate and analyse routinely collected laboratory data on a quarterly basis [4,5] provides an ideal opportunity to study the effect of treatment modality on these variables.

To explore the effect of treatment modality on laboratory variables, we studied the same patients longitudinally before and after a change in RRT modality. We studied two groups of modality changes, PD to HD (PD to HD) and dialysis to transplantation (PD+HD to TP). The effect of modality change from HD to PD could not be analysed due to the very small numbers of patients in this group.

Subjects and methods

Study design

This was a multi-centre/national, longitudinal observational study of patients on RRT whose renal centres were reporting data to UKRR during the study period.

Case definition

All patients on the UKRR database from 1 January 1997 to 31 December 2004 were considered for the study. Two groups of patients were studied: patients who spent at least 12 months on PD and who then changed to

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Laboratory variables were measured using standard laboratory techniques in each centre. PTH was measured using

Laboratory data for four quarters prior to modality change (quarter −4 to −1), quarter of modality change (quarter ‘0’) and four quarters after modality change were collected and analysed. Quarterly data are extracted from renal centre IT systems as the most recent available laboratory result within that quarter. Because the exact date of modality change could fall at any point within each quarter, it is possible that laboratory variables reported for quarter ‘0’ could include values earlier in that quarter, including some dates prior to the modality change. The dates of the laboratory tests are not extracted. No information is collected on the identity of the nephrologist responsible for the patient’s care. Variables studied were blood haemoglobin (Hb) concentration and serum ferritin, albumin, adjusted calcium, phosphate, parathyroid hormone (PTH), bicarbonate and cholesterol concentrations. Laboratory variables were measured using standard laboratory techniques in each centre. PTH was measured using the so-called intact PTH assays that would be expected to cross-react with some carboxy terminal forms of the molecule present at high concentration in patients with renal failure, e.g. PTH2-84 [6]. Two assays for serum albumin were in widespread use: BCG (bromocresol green) and BCP (bromocresol purple). Assay methods have significant influence on the results, particularly in PD patients where serum albumin results are in the lower concentration range [7,8]. The difference between the two assays has been shown to be non-proportional (i.e. a larger difference between the two methods at lower concentrations [9]), as has been confirmed by UKRR data (refer to Chapter 9 of the UKRR Annual Report 2000 [10]), and so these two groups of results were analysed separately after ascertainment of which assays had been in use in each centre during the relevant time frame. Calcium data were adjusted using the formula:

\[
\text{Adjusted calcium (mmol/L)} = \text{calcium} + \{40 - \text{albumin (g/L)}\} \times 0.02.
\]

irrespective of the albumin assay used.

Statistical analysis

Mixed models were used to obtain adjusted means of the laboratory variables for each of the four relative quarters before and after modality change and for the quarter when the change in modality took place. Age (continuous), gender, centre (43 centres) and year of change in modality (6 years) were included in the models. To accommodate the repeated measures’ structure of the data, we fitted the subject as a random effect. Pair-wise comparisons were made between the adjusted means for the different relative quarters using the Tukey method to correct for multiple testing. Further, as a large number of models were fitted, only P values of <0.001 were taken as strong evidence of a difference. Log transformation was used for serum ferritin and parathyroid hormone concentrations. Analyses were performed using proc mixed in SAS (version 8.2).

Results

During the study period, 1387 patients changed from PD to HD, of whom 495 (35.6%) died within the first year, leaving 892 for analysis. A total of 2147 dialysis patients underwent transplantation, of whom 114 (5.3%) died within the first year, leaving 2033 for analysis.

Patient characteristics

Table 1 summarizes baseline characteristics of study cohorts in each treatment change group and those who died within the first year, in each group. In each modality change group, when compared with the study cohort, those who died in the first year were older (P < 0.001 for both comparisons), and a higher proportion had diabetes mellitus as the primary renal diagnosis (P = 0.01 PD + HD to Tp; P = 0.03 PD to HD).

PD to HD group

Following modality change from PD to HD, mean Hb fell by 1.3 g/dL in the quarter in which the change occurred, and then gradually increased to a pre-transfer concentration of 11.3 g/dL by the fourth quarter (P < 0.001) (Figure 1A). Serum ferritin concentrations increased over four quarters from 287 µg/L to 382 µg/L (P < 0.001) (Figure 1B). Serum albumin concentrations increased after modality change (Figure 1C). Over four quarters, the mean concentration increased by 3.2 g/L in the BCG group and 3.4 g/L in the BCP group (P < 0.001). Adjusted serum calcium concentrations remained unchanged (P = 0.12). There was an increase in mean serum phosphate from 1.7 to 1.9 mmol/L (P < 0.001) during the first two quarters, and then the concentration plateaued (Figure 1D). Following change of modality, a linear increase in PTH was seen over four quarters (Figure 1E), bicarbonate fell by 3 mmol/L (from 26 to 23 mmol/L; P < 0.001) (Figure 1F) and the mean cholesterol fell over the four quarters after change of modality by almost 1 mmol/L (5.4–4.3 mmol/L; P < 0.001) (Figure 1G).

PD + HD to Tp group

Following renal transplantation, mean Hb showed a rise of 2 g/dL by the end of the fourth quarter (P < 0.001) (Figure 1A). The maximum rate of increase was seen in the first quarter (11.2–12.6 g/dL). Mean serum ferritin fell from 250 to 120 µg/L by the end of the fourth quarter.
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Fig. 1. (A) Haemoglobin by quarter before and after modality change (with lines showing 95% CI). (B) Serum ferritin by quarter before and after modality change (with lines showing 95% CI). (C) Serum albumin by quarter before and after modality change (with lines showing 95% CI). (D) Serum phosphate by quarter before and after modality change (with lines showing 95% CI). (E) Serum PTH by quarter before and after modality change (with lines showing 95% CI). (F) Serum bicarbonate by quarter before and after modality change (with lines showing 95% CI). (G) Serum cholesterol by quarter before and after modality change (with lines showing 95% CI). (P < 0.001) (Figure 1B). There was a rise in the mean serum albumin concentration, and by the fourth quarter, this had increased by 3.0 g/L in the BCG group and by 3.6 g/L in the BCP group (P < 0.001) (Figure 1C). Most of the increase occurred during the first two quarters following transplantation, although it continued to rise throughout the follow-up period. Serum-adjusted calcium concentration remained unchanged after transplantation. The mean serum phosphate concentration fell to normal within 3 months of transplantation (1.9–0.9 mmol/L; P < 0.001) (Figure 1D). The mean PTH concentration fell rapidly in the first 6 months from 16 pmol/L to 8 pmol/L, although it remained above the normal reference range (usually <8 pmol/L, depending on the laboratory) at the end of the fourth quarter (P < 0.001) (Figure 1E). The serum bicarbonate concentration increased by 1 mmol/L (24–25 mmol/L) (Figure 1F). The mean cholesterol concentration increased by 0.5 mmol/L in the first quarter following transplantation (5–5.5 mmol/L; P < 0.001), and then fell over the next three quarters (Figure 1G).

Discussion

This is the first large-scale longitudinal study analysing the effect of RRT modality change on laboratory variables. Suzuki et al., in 2003, studied the influence of mode of dialysis (PD versus HD) in a small group of 36 matched patients and reported that patients on PD had lower blood pressures and higher cholesterol concentrations than matched patients on HD; no other significant differences in laboratory variables were found [11]. The strengths of our analysis lie in the size of the cohorts studied (892 in PD to HD group and 2033 in HD + PD to Tp group) and the longitudinal paired
nature of the data. As the same patients were studied sequentially, the effect of individual patient characteristics on different variables is nullified and hence any change would likely be a function of treatment modality. We were unable to study the effect of modality change from HD to PD as data were insufficient. The UKRR has shown that ∼3% of patients stabilized on HD change to PD in the first year and almost none change thereafter [12].

**Peritoneal dialysis to haemodialysis**

In all comparisons, it is important to remember that samples for laboratory tests are taken prior to a HD session, and therefore do not reflect steady state concentrations in HD patients as they do in PD patients. Even for haemoglobin and ferritin, dilution caused by extra cellular fluid expansion would be expected to cause slightly lower concentrations pre-dialysis. Changes in serum calcium concentration depend on dialysate calcium concentration. Serum phosphate concentration falls during HD [13].

The fall of haemoglobin following modality change is likely to be multi-factorial. The important factors that can explain the drop in haemoglobin are loss of residual renal function after starting HD, loss of blood during initial unstable period of HD and short-term resistance to erythropoiesis-stimulating agents (ESA) as peritonitis remains the primary cause of transfer from PD [14–17]. There is also evidence of higher ESA dose requirements on HD compared to PD [18,19]; in a previous UKRR analysis, 77% of prevalent PD patients were receiving ESAs compared to 91% of HD patients, with a lower median weekly dose (equivalent to 5000 units/week epoetin alfa or beta on PD versus 8000 units/week on HD) with similar haemoglobin concentrations [20]. Lack of anticipation of a higher ESA requirement with HD would aggravate this fall in Hb concentration. We suggest that ESA should be commenced or the dose should be increased at the time of modality switch. In centres utilizing algorithms for ESA prescription, this should be incorporated. Our analyses also show that it took a full year for this cohort of survivors to reach their pre-transfer Hb concentrations. During this time, ferritin concentrations increased substantially. Although an initial rise in serum ferritin concentration could be an acute phase response, given that peritonitis is a common cause of transfer from PD to HD, this would not explain the higher concentrations 6 months after change of modality. Easy accessibility to iron administration in HD units could be a contributory factor for a rise in ferritin concentrations.

Serum albumin concentration is influenced by assay methods used by the laboratories [8]. In the UK, albumin is measured by two different assays, bromocresol purple (BCP) and bromocresol green (BCG). The BCG assay overestimates albumin when compared with the BCP assay that is close to the gold standard antibody-based methods. BCG gives serum albumin results ∼5 g/L higher on average than BCP in renal patients [21,22]. Following modality change from PD to HD, an increase in the four-quarter mean by 3.2 g/L in the BCG group and 3.4 g/L in the BCP group was seen. Improvement was noticed immediately following switch. This rise could be explained on the basis of fall in peritoneal protein losses and reduction in extra cellular fluid volume with gradual achievement of target weight.

Serum-adjusted calcium concentration did not change significantly with modality switch. Serum phosphate showed a significant small rise of 0.2 mmol/L in the first two quarters, and then the concentration plateaued. This rise could be mainly because of the pre-HD sampling of blood than actual increase in average serum phosphate. The progressive rise in PTH following change from PD to HD is a new finding and remains unexplained. Previous studies have shown similar skeletal responsiveness to PTH in HD compared to PD patients [23–25], although one study has suggested that PD is a risk factor for the development of adynamic bone disease [26]. The rise in PTH seems unlikely to be due to the minor rise in predialysis serum phosphate concentration. Glomerular filtration plays a crucial role in the clearance of PTH and especially the carboxy-terminal forms of PTH [27]. If RRF is lost when switching from PD to HD (as either the cause of the consequence of modality change), then renal clearance of PTH (and its biologically inactive fragments) will likely also decrease. Also, PTH and its fragments are potentially better cleared across the peritoneal membrane than across dialysis membranes, given the superior middle molecule clearance seen in PD. Loss of residual renal function causing further reduction in 1α-hydroxylation of vitamin D may also have contributed.

The fall in serum cholesterol concentration following change from PD to HD could be due to withdrawal of PD solutions or to systemic inflammation induced by HD; this finding is consistent with previous cross-sectional comparisons of HD and PD.

In summary, switching dialysis modality has a significant effect on a number of blood test results. Whilst some of these effects can be explained by the short-term factors associated with the reason for switching, many persist and are thus likely to be an effect of the modality itself. Dialysis modalities (PD and HD) have a significant effect on haemoglobin, ferritin, albumin, cholesterol and PTH. These modalities do not have any significant effect on calcium and phosphate concentrations. This raises questions about same standards of achievement for the two dialysis modalities.

**Dialysis to transplantation**

Renal transplantation restores kidney functions and hence, as expected, had a favourable effect on laboratory variables. Our analysis shows improvement in haemoglobin, albumin, phosphate and PTH concentrations. Though there was a fall in PTH concentrations following renal transplantation, even at the end of 1 year, PTH concentrations remained above higher limits of normal concentration. Renal transplantation did not completely normalize serum PTH concentration. We conclude that spontaneous resolution of hyperparathyroidism after transplantation is uncommon. In this study, this could be partly due to the level of graft function in the cohort. As in the PD to HD group, an improvement in serum albumin concentration was seen immediately. The early rise followed by gradual fall in serum cholesterol concentrations could be due to the effects of immunosuppressive medications on lipid metabolism followed by the introduction of cholesterol-lowering therapy.
Limitations

General cautions and limitations applicable to any registry data analysis are applicable to this analysis. At present, UKRR does not hold record for reasons of modality switch from PD to HD. Hence further analysis by reason for the modality change could not be done. Such analysis could have given insight into changes in the albumin and ferritin concentrations in the dialysis group. In this study, as only those who survived for at least 12 months after modality change were included, a significant survival pressure should be born in mind while generalizing the observations. Both cohorts only included patients who survived at least a year after the change in modality. As would be expected, the death rate was higher in the PD to HD cohort compared to the PD + HD to Tp cohort, but the purpose of this analysis is not to compare the extent of the changes seen after the modality change between these two cohorts, but within each cohort. The advantage of this approach is that it minimizes the confounding effect of intermittent illness associated with the modality switch and there is evidence that individuals surviving a year revert to their baseline overall mortality risk [28]. Drug therapy has a considerable influence on several of the variables analysed, but we have no data on drug therapy, for instance with ESA, cholesterollowering drugs or phosphate binders.

Graft function is likely to have an important influence on other laboratory variables after transplantation but has not been included as an outcome or explanatory variable here. Previous reports have shown a wide range of graft function amongst UK transplant recipients [29]: it is possible that poor graft function is responsible for some of the persistent biochemical abnormalities seen in this group, including persistent hyperparathyroidism.

It is possible that changes in laboratory variables were a result of changes in practice by different nephrologists. While in the UK it is a common practice for nephrologists to provide continuous care for patients on both dialysis modalities, it is possible that some of the differences observed were due to changes in nephrologist providing the care, but it is unlikely that these differences would be all in one direction. Similarly, patients undergoing transplantation may often come under the care of a nephrologist in a transplant centre, but we consider it unlikely that this change is primarily responsible for the changes reported here. While it might have been of interest to examine the changes following transplantation for HD and PD patients separately, we have shown (unpublished) that the magnitude and direction of the changes are similar.

Conclusions

From this study we conclude that different modalities of renal replacement therapy have different effects on laboratory variables. In a given patient when treatment modality is switched from PD to HD, a drop in haemoglobin concentration of 1.0–1.5 g/L should be anticipated. We suggest appropriate steps should be taken early in the course of modality change to negate this effect. Although renal transplanta-

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Conflict of interest statement. None declared.

References

Effects of endurance training on extrarenal potassium regulation and exercise performance in patients on haemodialysis

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Abstract

Background. Haemodialysis patients (HDP) with anaemia display impaired plasma $K^+$ regulation during exercise and poor exercise performance. Epoetin treatment and exercise training improve exercise performance in HDP, but whether this is associated with improved $K^+$ regulation is unknown.

Methods. Six HDP with near-normal [Hb] were tested for aerobic power (VO\textsubscript{2peak}) and plasma [K\textsuperscript{+}] during incremental exercise; quadriiceps muscle strength (peak torque, PT) from 0 to 360° s\textsuperscript{-1} and fatiguability (decline in strength during thirty contractions). Tests were conducted at baseline, after 6 weeks of normal activity (pre-train) and following 6 weeks cycle training (post-train). Six healthy untrained controls (CON) matched for age, sex, mass and height were tested at baseline.

Results. In HDP at baseline, VO\textsubscript{2peak} and PT from 0 to 360° s\textsuperscript{-1} were respectively reduced by 37% and 27–42%, compared to CON ($P < 0.05$). Plasma [K\textsuperscript{+}], the rise in [K\textsuperscript{+}] (Δ[K\textsuperscript{+}]) and the Δ[K\textsuperscript{+}] relative to total work done (Δ[K\textsuperscript{+}] work\textsuperscript{-1} ratio) during incremental exercise were all higher in HDP at baseline compared to CON ($P < 0.05$).

Exercise training increased time to fatigue by 12% ($P < 0.05$) but did not improve $K^+$ regulation or VO\textsubscript{2peak}. An inverse correlation was found between the $\Delta[K^+]$ work\textsuperscript{-1} ratio and VO\textsubscript{2peak} for pooled CON and HDP data.

Conclusions. In HDP treated with epoetin, poor exercise performance was related to impaired extrarenal $K^+$ regulation, whilst training improved exercise performance but not $K^+$ regulation. Thus, although impaired extrarenal $K^+$ regulation may contribute to poor exercise performance in HDP, exercise performance can still improve with training despite unchanged $K^+$ regulation.

Keywords: exercise training; haemodialysis; muscle strength; potassium regulation; VO\textsubscript{2peak}

Introduction

Haemodialysis patients (HDP) display abnormally low exercise performance, with peak oxygen consumption during incremental exercise (VO\textsubscript{2peak}) and muscle strength each