Management of anaemia in United Kingdom renal units: a report from the UK Renal Registry

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Abstract

**Background.** Morbidity and mortality of patients undergoing renal replacement therapy is influenced by the adequacy of correction of renal anaemia. The Renal Association has set standards for attainment of a target haemoglobin of 10 g/dl. This study compared the management of anaemia in dialysis patients in nine renal units in the UK.

**Methods.** A cross-sectional analysis was carried out on data submitted electronically to the UK Renal Registry. There were 1449 haemodialysis patients and 741 peritoneal dialysis patients in the nine renal centres analysed. Individual patient data were collected on haemoglobin, ferritin, erythropoietin prescription, and pre- and post-dialysis urea concentrations.

**Results.** None of the centres achieved the standard of more than 80% of haemodialysis patients with a haemoglobin of greater than 10 g/dl. Three centres achieved this standard for peritoneal dialysis. There was wide variation between centres in the percentage reaching the target. Differences in ferritin, erythropoietin prescription, and dialysis doses between centres could not entirely explain the variations between centres. Females had lower haemoglobin than males despite a greater proportion being treated with erythropoietin. There was a trend of increasing haemoglobin concentration during the study period in haemodialysis but not in peritoneal dialysis patients.

**Conclusions.** The Renal Association standards for management of anaemia are not being met. The data allow renal centres to compare their practices with others to identify areas that might be improved. Further analysis may allow a benchmark to be determined of what it is possible to achieve by best practice.

**Subjects and methods**

Details of the methods employed by the Renal Registry are given in the First Annual Report, 1998 [16]. Data were collected electronically each quarter from the nine participating centres that had sent a complete set of data to the Registry throughout 1997. All patients had been undergoing treatment with the same modality of dialysis for more than 90 days. Haematological and biochemical data were the latest available in the last 6 months of 1997. Pre-dialysis
haemoglobin was used in haemodialysis patients. For sequential analysis, haemoglobin concentration in the first quarter of 1997 was compared to that in the last quarter. There were 1449 patients on haemodialysis and 741 on peritoneal dialysis with haemoglobin data available. Anonymity of the centres is an important principle of the Registry. Whilst the number of participating centres is small, identification of the centre by the number of patients they dialyse is possible and therefore results for individual centres are reported as percentages. The number of patients in each centre ranged from 63 to 256 for haemodialysis patients and 29 to 226 for peritoneal dialysis.

The data collected were haemoglobin concentration, serum ferritin, and pre- and post-haemodialysis urea concentrations to allow calculation of urea reduction ratio as a measure of delivered dialysis dose. The technique for post-dialysis urea sampling was not standardized between centres. Age, gender, duration of renal replacement therapy, and the prescription of erythropoietin were recorded.

Statistical analysis

Analyses were performed by a biostatistician using the SAS statistical package. For individual centres, median haemoglobin with upper and lower quartiles was reported. Where appropriate means and 95% confidence intervals are also given. In the assessment of the significance of age and duration of renal replacement therapy on haemoglobin concentration, Spearman’s correlation was used since it detects any increasing or decreasing relationship rather than specifically linear relationships. The effect of gender was compared using two sample t-tests. The cumulative frequency distribution graphs were smoothed using a cubic spline algorithm [17], which may result in discrepancy between reading a figure from the graph and the figure listed in the comparable table. To take account of differences in demography between units, analysis of variance was used to calculate the mean haemoglobin adjusted for age, gender, and length of time on treatment, and also polycystic kidney disease, which is known to be associated with higher haemoglobin.

Results

Attainment of Renal Association standards for haemoglobin

As shown in Table 1 no centre achieved the 1995 Renal Association standard of 80% attainment of target haemoglobin for haemodialysis patients, although the 95% confidence interval for centres D and I crossed the standard level. Data from centre I should be viewed with caution as the proportion of patient data returned was lower than from other centres. Three centres reached the standard for peritoneal dialysis patients (Table 2). In each of these the 95% confidence interval crossed below the standard level. In an additional four centres, whilst the median was below the standard, the 95% confidence interval crossed above it.

The distribution of haemoglobin concentrations for patients on haemodialysis and peritoneal dialysis are shown in Figure 1. The shape of the distribution of haemoglobin concentrations was similar regardless of the median haemoglobin achieved. From the relationship between median haemoglobin and percentage of patients reaching the target, shown in Figure 2, it can be estimated that to achieve the 1997 standard of 85% with haemoglobin over 10.0 g/dl would require a median haemoglobin of 11.5 g/dl.

Effect of age, change of dialysis modality, gender, and duration of renal replacement therapy

Change of dialysis modality was associated with reduction in haemoglobin, justifying the exclusion from the rest of the analysis of patients who had not been stable on a mode of dialysis for more than 3 months. Change from peritoneal dialysis to haemodialysis was associated with a 1.7 g/dl reduction in mean haemoglobin (95% CI 1.0–2.5, P < 0.0001). Change from haemodialysis to peritoneal dialysis was associated with a 1.2 g/dl reduction in mean haemoglobin (95% CI 0.6–1.9, P = 0.0002).

A statistically significant correlation between age and haemoglobin concentration was found in peritoneal dialysis patients, but the correlation coefficient was weak (r = 0.1, P < 0.009). In haemodialysis no significant correlation was found (r = −0.04, P = 0.09). No linear trend was found between erythropoietin prescription and age. Men had significantly higher haemoglobin concentrations than women on both haemodialysis and peritoneal dialysis (Table 3). There was no evidence to suggest under-prescribing of erythropoietin in men compared to women, as overall more females were on erythropoietin than males. There was no significant difference in erythropoietin prescribing to males and females with a haemoglobin less than 10.0 g/dl.

Statistically significant but weak correlations were found between haemoglobin and length of time on renal replacement therapy (haemodialysis: r = 0.14, P < 0.0001; peritoneal dialysis: r = −0.11, P = 0.004). The proportion of patients requiring erythropoietin therapy increased with time on renal replacement treatment (Table 4). A plateau was reached in haemodialysis around the second year of renal replacement therapy, whilst in peritoneal dialysis erythropoietin use increased more slowly, probably due to reduced rate of loss of residual renal function. Comparison of data in Table 1 with Table 2 shows that a higher proportion of peritoneal dialysis patients with haemoglobin less than 10.0 g/dl are not on erythropoietin compared with haemodialysis patients, indicating a relative reluctance to prescribe erythropoietin to peritoneal dialysis patients. The dose of erythropoietin prescription was not available in the Renal Registry.

As expected, diagnosis affected achieved haemoglobin, and patients with polycystic kidney disease had higher haemoglobin than patients with other diagnoses (difference in haemodialysis, 1.0 g/dl, 95% CI 0.7–1.4 g/dl, P < 0.0001; difference in peritoneal dialysis, 0.9 g/dl, 95% CI 0.5–1.4 g/dl, P < 0.0001). To investigate whether differences in age, gender, duration of treatment, or polycystic kidney disease could explain the differences in mean haemoglobin achieved at the
Table 1. Haemoglobin, use of erythropoietin, serum ferritin, and urea reduction ratio in haemodialysis patients

<table>
<thead>
<tr>
<th>Unit</th>
<th>% Return</th>
<th>Median Hb (g/dl)</th>
<th>Quartile range</th>
<th>% Hb ≥ 10 g/dl (95% CI)</th>
<th>% Hb ≥ 10 g/dl without Epo</th>
<th>% Ferritin ≥ 100 ng/ml</th>
<th>% on Epo with Hb &lt; 10.0 g/dl</th>
<th>URR ≥ 65%</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>88</td>
<td>10.2</td>
<td>8.9–11.4</td>
<td>56 (48–64)</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>58</td>
</tr>
<tr>
<td>B</td>
<td>86</td>
<td>9.8</td>
<td>8.5–10.6</td>
<td>43 (31–57)</td>
<td>26</td>
<td>86</td>
<td>33</td>
<td>90</td>
</tr>
<tr>
<td>C</td>
<td>98</td>
<td>9.4</td>
<td>8.5–10.7</td>
<td>37 (29–46)</td>
<td>9</td>
<td>72</td>
<td>74</td>
<td>43</td>
</tr>
<tr>
<td>D</td>
<td>94</td>
<td>11.4</td>
<td>10.2–12.7</td>
<td>78 (72–83)</td>
<td>20</td>
<td>79</td>
<td>77</td>
<td>92</td>
</tr>
<tr>
<td>E</td>
<td>97</td>
<td>10.6</td>
<td>9.5–11.7</td>
<td>65 (59–71)</td>
<td>28</td>
<td>*</td>
<td>61</td>
<td>73</td>
</tr>
<tr>
<td>F</td>
<td>100</td>
<td>10.6</td>
<td>9.6–11.5</td>
<td>70 (64–75)</td>
<td>20</td>
<td>81</td>
<td>76</td>
<td>90</td>
</tr>
<tr>
<td>G</td>
<td>100</td>
<td>10.4</td>
<td>9.2–11.4</td>
<td>59 (51–67)</td>
<td>na</td>
<td>91</td>
<td>na</td>
<td>53</td>
</tr>
<tr>
<td>H</td>
<td>96</td>
<td>10.4</td>
<td>9.3–11.8</td>
<td>60 (54–66)</td>
<td>8</td>
<td>93</td>
<td>86</td>
<td>92</td>
</tr>
<tr>
<td>I</td>
<td>59</td>
<td>10.9</td>
<td>10.0–11.7</td>
<td>76 (62–87)</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>*</td>
</tr>
<tr>
<td>Total</td>
<td>94</td>
<td>10.5</td>
<td>9.3–11.7</td>
<td>62 (60–65)</td>
<td>18</td>
<td>84</td>
<td>73</td>
<td>58</td>
</tr>
</tbody>
</table>

a, Not available; —, Not applicable; * <75% data return.

Effect of serum ferritin, erythropoietin prescription, and dialysis quality on haemoglobin

Erythropoietin prescription, iron stores, and dialysis quality are thought to influence haemoglobin. The proportion of patients who do not require erythropoietin treatment to maintain a haemoglobin greater than 10.0 g/dl may be a useful indicator of whether the overall management within a centre is conducive to high or low haemoglobin. Figure 3a shows that there may be a relationship between achievement of urea reduction ratio of greater than 65% and the proportion of patients with haemoglobin concentration spontaneously greater than 10.0 g/dl. However, given the small number of centres with adequate data, formal statistical analysis has not been performed. Similarly, Figure 3b shows that the proportion of patients on erythropoietin may be inversely related to the proportion with good urea clearance, although many other factors (for example, finance) influence erythropoietin prescription and this is therefore difficult to interpret. The small numbers and broad confidence intervals mean that statistically valid comparison is difficult, but individual centres may wish to use the information in Tables 1 and 2 to compare their practice with others. For instance, haemodialysis patients in centre B have a high proportion of patients not requiring erythropoietin treatment to maintain a haemoglobin greater than 10.0 g/dl, but a low attainment of the target haemoglobin, likely to be due to a low level of erythropoietin prescribing. Centre D achieved the highest median haemoglobin in haemodialysis patients despite only average achievement of all the other measures. The attainment of the target was higher in centre D than in centre F, although the other measures were virtually identical in the two centres, demonstrating that these measured variables cannot entirely explain achieved haemoglobin. Similar analyses can be made for peritoneal dialysis, although the data set is less complete.

Changes in haemoglobin with time
Sequential data were only available for 1 year and analysis of changes over time was limited. Differences
Fig. 1. Frequency distribution plots of haemoglobin for (a) haemodialysis patients and (b) peritoneal dialysis patients in nine UK renal centres. The curves for each centre were smoothed using a cubic spline algorithm.

In attainment of the haemoglobin standard between the first and last quarters of 1997 are shown in Figure 4. For haemodialysis, only one centre did not increase the proportion of patients achieving the standard. Peritoneal dialysis patients started the year with higher haemoglobins than haemodialysis patients but in several centres attainment of the standard declined through the year.
Fig. 2. Relationship between median haemoglobin and percentage of patients with haemoglobin above 10 g/dl in each centre; • haemodialysis, ● peritoneal dialysis.

Discussion

The UK Renal Association has set desirable standards for attainment of a target haemoglobin (10.0 g/dl). European Best Practice Guidelines for the management of anaemia in patients with chronic renal failure have recently been published suggesting a target haemoglobin concentration of 11.0 g/dl [18]. In 1995 the Renal Association set 80% achievement of the target haemoglobin as the standard, this was increased to 85% in 1997. The European guidelines also suggest a minimum standard of 85% achievement of their higher target. Despite the setting of these standards, the benchmark proportion of a dialysis population that could reasonably be expected to achieve the targets by best practice is not known.

There are some patients, for example those with homozygous sickle-cell anaemia [19], for whom a haemoglobin over 10.0 g/dl is deleterious. High haemoglobin concentration might also increase the risk of vascular access thrombosis and cardiovascular events. Intercurrent illness and erythropoietin resistance mean that some patients will inevitably fall below the target. It is not known how long it can be expected to take for a new uraemic patient to reach the target haemoglobin once treatment has started. It is possible that individual centres set different targets for themselves as governed by local issues such as finance but this information is not available to the registry.

The registry data show that changes of dialysis modality from haemodialysis to peritoneal dialysis or vice versa were associated with a fall in haemoglobin. This might be expected for a change to haemodialysis but is more surprising for a change to peritoneal dialysis. Since change of modality is most often precipitated by a problem with the dialysis or an intercurrent illness, it is likely that the underlying problem is the cause of a fall in haemoglobin rather than its being due solely to the change of dialysis technique.

The proportion of patients achieving the target haemoglobin varied widely between centres. Of the demographic factors examined, only gender and diagnosis of polycystic kidney disease had a clinically significant effect on haemoglobin concentration. The proportion of patients with ferritin levels over 100 ng/ml varied widely between units. The Renal Association has not set a standard for intravenous iron use.

In the normal population, females have lower haemoglobin than males, probably due to androgen production by males. This difference is maintained in the dialysis population, despite no gender difference in the target haemoglobin. A higher proportion of females than males was treated with erythropoietin. Since females naturally have a lower haemoglobin, it is possible that the difference in proportion treated with erythropoietin should be even greater. To ensure that there was no discrimination against females in erythropoietin prescribing we examined those with haemoglobin less than 10.0 g/dl. For both males and females, these patients would be expected to be prescribed erythropoietin in an attempt to achieve the target. Amongst this group, there was no significant difference between males and females, demonstrating no evidence of underprescribing of erythropoietin to females. Whether the optimum haemoglobin for males and females is the same is unknown. Since there is no difference in the target haemoglobin for males and females it should be recognized that it may be more difficult to reach the standard in females.

Adjustment for differences in age, gender, duration of dialysis and diagnoses between centres did not

Table 3. Haemoglobin and erythropoietin prescription in males and females on dialysis

<table>
<thead>
<tr>
<th></th>
<th>Mean Hb g/dl (95% CI)</th>
<th>% on erythropoietin</th>
<th>Hb &lt;10.0 g/dl % on erythropoietin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemodialysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>10.7 (SD 1.8)</td>
<td>69.5</td>
<td>77</td>
</tr>
<tr>
<td>Females</td>
<td>10.2 (SD 1.6)</td>
<td>77.9</td>
<td>82</td>
</tr>
<tr>
<td>Difference (95% CI)</td>
<td>0.45 (0.27 to 0.64)</td>
<td>−8.3 (−13.5 to −3.2)</td>
<td>−4.7 (−12.5 to +3.2)</td>
</tr>
<tr>
<td></td>
<td>P&lt;0.0001</td>
<td>P=0.0003</td>
<td>P=0.3</td>
</tr>
<tr>
<td>Peritoneal dialysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>11.3 (SD 1.7)</td>
<td>43.4</td>
<td>45</td>
</tr>
<tr>
<td>Females</td>
<td>10.7 (SD 1.5)</td>
<td>55.4</td>
<td>60</td>
</tr>
<tr>
<td>Difference (95% CI)</td>
<td>0.57 (0.34 to 0.81)</td>
<td>−12.0 (−20.0 to −3.8)</td>
<td>−15.4 (−31.8 to +1.0)</td>
</tr>
<tr>
<td></td>
<td>P&lt;0.0001</td>
<td>P=0.0006</td>
<td>P=0.1</td>
</tr>
</tbody>
</table>
Fig. 3. Relationship between the percentage of haemodialysis patients achieving a urea reduction ratio of 65% and (a) percentage of patients with haemoglobin concentration spontaneously over 10 g/dl and (b) percentage of patients prescribed erythropoietin. Data on erythropoietin prescribing was available from six centres.

Fig. 4. Changes in percentage of patients on (a) haemodialysis and (b) peritoneal dialysis with haemoglobin over 10 g/dl between 1st and 4th quarter of 1997.

Table 4. Changes in rate of erythropoietin prescribing with time on renal replacement therapy

<table>
<thead>
<tr>
<th>Modality</th>
<th>Percentage on erythropoietin by years on renal replacement therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 1 year</td>
</tr>
<tr>
<td>Haemodialysis</td>
<td>59</td>
</tr>
<tr>
<td>Peritoneal dialysis</td>
<td>35</td>
</tr>
</tbody>
</table>

noticeably alter the variability in mean haemoglobin, which is therefore likely to be due to differences in aspects of management. Differences between centres were not tested statistically because numbers in each centre are small whilst the number of possible comparisons is large. Nevertheless, individual centres will find comparison with others useful in assessing their own practice. In every centre, it was possible to identify changes in management that might increase haemoglobin levels. Unfortunately, reliable data on erythropoietin prescribing is difficult to achieve, as the information has to be loaded manually for each patient. Erythropoietin prescription and particularly dosage vary frequently and as yet it has not proved possible for the registry to collect useful data on erythropoietin dosing. It is hoped that this will improve in the future.

The proportion of haemodialysis patients reaching the target increased during 1997. In several centres haemoglobin concentration of peritoneal dialysis patients declined during the year, albeit from a higher level than achieved for haemodialysis patients. The relative underprescribing of erythropoietin to peritoneal dialysis patients may be because they are mainly treated at home and usually have to administer their own erythropoietin, whereas haemodialysis patients more often attend centres where erythropoietin can be given to them. Underprescribing to peritoneal dialysis patients suggests that it should be possible to improve their haemoglobin further.

With current practice the shape of the distribution of haemoglobin concentrations was similar regardless of median haemoglobin. The data suggests that to achieve the target of 85% of patients with haemoglobin over 10.0 g/dl requires a median for the population of
around 11.5 g/dl. This implies a significant proportion of patients with a haemoglobin concentration above this level. Adopting the new European guideline target of 11.0 g/dl will inevitably raise the median haemoglobin still higher. Whether this can be achieved most effectively by a centre-wide policy such as giving intravenous iron to all patients or by targeting individuals is yet to be proven. Since a high haemoglobin may be harmful to some it is important to ensure that in attempting to reach the standards for a population, the interests of individual patients are not compromised.

An individual’s haemoglobin concentration is an interaction between a number of variables, some of which can be measured and are amenable to intervention. Analysis of data submitted to the UK Renal Registry provides insights into the interactions involved. Renal centres, by comparison with others, can use the data to examine their own practice and identify areas that might be improved.

References

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