Haemoglobin level and vascular access survival in haemodialysis patients

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Abstract

Background. A full correction of anaemia in haemodialysis (HD) patients may lead to an increased risk of vascular access (VA) failure. We studied the relationship between haemoglobin (Hb) level and VA survival.

Methods. Incident patients between January 2000 and December 2002 with <1 month on HD were considered. The relative risk (RR) of access failure was evaluated in four different groups of patients divided according to their Hb level (<10, 10–12, 12–13 and >13 g/dl). Other factors possibly influencing VA survival were also considered: age, gender, diabetes, vascular disease, intact parathyroid hormone (iPTH) and treatment with an angiotensin-converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB) or recombinant human erythropoietin therapy.

Results. We studied 1254 patients (1057 with autologous fistulae, 75 grafts and 122 permanent catheters at admission). Based on Cox analysis, we found the next statistically significant RR of VA failure to be 2.3 times higher with grafts than with arterio-venous fistulae (AVFs) and 1.8 times higher in AVFs with Hb <10 g/dl than in AVFs of the next Hb group. There was no statistically significant difference in the RR of VA failure between patients with Hb 10–12 g/dl and those with Hb 12–13 g/dl or >13 g/dl. Diabetes (RR: 1.41, \( P = 0.06 \)), age >65 years (RR: 1.32, \( P = 0.11 \)) and iPTH (RR: 1.56; \( P = 0.01 \)) were identified as predictive factors for VA failure; ACE inhibitors or ARB (RR: 0.69; \( P = 0.03 \)) were found to be protective factors.

Conclusions. In the studied population, the correction of Hb level to >12 g/dl was not associated with a higher incidence of VA thrombosis than in patients with Hb between 10 and 12 g/dl. ACE inhibitors or ARBs were found to be protective factors, and diabetes, age >65 years and iPTH >400 pg/ml were negative predictive factors for VA survival.

Keywords: ACE inhibitors; anemia correction; Diabetes Mellitus; haemoglobin; iPTH; vascular access

Introduction

Anaemia is a characteristic and important clinical manifestation of progressive renal disease. It usually worsens with the development of renal failure and it can be corrected with recombinant human erythropoietin (rHuEPO).

Although rHuEPO has been used in dialysis patients since 1989, there is not yet a global consensus regarding the optimum haematocrit target in this patient population. Indeed, the appropriate target haematocrit for dialysis patients has throughout the last decade been one of the most debated issues in nephrology.

Guidelines have suggested a target haemoglobin (Hb) >11 g/dl, with an average value of 12–12.5 g/dl (European Best Practice Guidelines) [1] and a haematocrit of 33–36% (Hb 11–12 g/dl; NKF-DOQI Guidelines) [2]. However, many studies have shown that by maintaining the Hb of dialysis patients at nearly normal levels, great advantages in terms of quality of life [3], cardiac function [4], brain function [5], hospitalization and cost [6] can be achieved without significant adverse effects. Nevertheless, there has been some concern that full correction of anaemia may increase the risk of adverse effects, such as vascular access (VA) thrombosis, in dialysis patients [7]. The aim of this study was to determine if there is any relationship between Hb levels and VA survival. As secondary aims, other variables were examined to analyse their influence on VA survival: diabetes, age, gender, vascular disease (cerebrovascular disease, cardiovascular disease and limb amputation) and intact parathyroid
hormone (iPTH) at admission, and treatment with an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB) and rHuEPO during follow-up.

**Patients and methods**

**Subjects**

Data for this study were collected in 40 dialysis units of the Fresenius Medical Care Provider, Spain, by the European Clinical Database (EuCliD) [8]. This database prospectively gathers demographic and clinical information on all end-stage renal disease (ESRD) patients admitted to haemodialysis (HD), and it is continuously updated. It contains detailed information on VA with respect to VA surgery date, type of access, access site, date of failure and all access-related complications.

We selected 1254 incident patients who had been on renal replacement therapy for < 1 month who started HD with a permanent VA between January 2000 and December 2002. Patients with either autologous fistulae (AVFs) or artificial grafts were considered. Patients with catheters were not included in all analyses, because catheters are also occasionally used as temporary VA.

**Study variables and outcome definitions**

The patients were categorized into four groups based on their mean Hb levels during follow-up: <10 g/dl; 10–12 g/dl; 12–13 g/dl and >13 g/dl, and they were examined for their VA survival and relative risk (RR) of access failure.

To test the predictive role of Hb level, survival analyses were conducted using the date of first venipuncture for the initiation of HD as time zero. For this reason, only patients starting dialysis in the participating dialysis centres were selected; and those starting dialysis with a temporary catheter were excluded. Vascular access survival was defined as the length of the intervention-free period to first failure. Permanent catheter failure was considered when it was removed for any reason.

Covariates selected a priori as possible risk factors for VA failure included age at the beginning of HD, gender, diabetic status and vascular disease (cerebrovascular disease, cardiovascular disease and limb amputation). These conditions were defined based on the International Classification of Diseases, Tenth Revision. For example, patients were considered to have ischaemic heart disease or cerebrovascular disease if they had an associated diagnosis falling under I20–I25 or under I63–I69, respectively. Diabetes, type 1 or 2, was confirmed likewise, irrespective of the underlying renal disease.

The presence of increased baseline levels of iPTH (>400 pg/ml), rHuEPO therapy or anti-hypertensive therapy based on ACE inhibitors or ARBs were considered as possible risk factors for access failure.

**Statistical analyses**

Survival functions were described using the Kaplan–Meier technique. The log-rank test was used for univariate comparisons. Patients were censored when changed to peritoneal dialysis, transferred to another dialysis unit, or if they received kidney grafts, they died or had a functioning VA on the final observation date (December 31, 2002). Cox’s proportional hazards regression was used to model time to event as a function of Hb level.

The potential effect of the type of VA (fistula, graft or permanent catheter) was evaluated both testing the effect of this covariate and stratifying the models. Risk factors related to patient demographics and co-morbid conditions were also considered. All variables used in the equations were chosen a priori and retained in the models if there was biological plausibility or if univariate analyses suggested that they might be associated with the event or might confound the relationship between the covariate of interest and the event. The proportional hazards assumption was checked for each model by inspection of the complementary log-minus-log plots. A stepwise method was employed to obtain the best multivariate model. The –2 log likelihood ratio (–2 Log L) statistics were used for goodness of fit comparisons [8,9]. Estimated RRs and the hazards ratios (HR) for time to event analyses and their 95% confidence intervals (95% CIs) were calculated using estimated regression coefficients and their standard error. The contribution of covariates to explain the dependent variable was assessed by means of a two-tailed Wald test, with P < 0.05 considered significant. The P-value for variable removal within the multivariate analyses was set to 0.10. All statistical analyses were performed using SPSS software, version 11 (SPSS Inc., Chicago, IL).

**Results**

We studied 1254 patients, of whom 1057 had autologous fistulae (84.6%) at admission, 75 (5.9%) had grafts and 122 (9.5%) had permanent catheters. The population characteristics of the patients with AVFs and grafts, respectively, are shown in Table 1.

A significantly higher proportion of females and diabetics were found among the patients with grafts. In the same group, significantly more patients turned out to have high iPTH levels and to be on rHuEPO therapy. We found no significant differences between patients with AVF and those with grafts for the proportion of elderly patients, patients on ACE inhibitors or ARBs as well as for patients with vascular disease, even when considering cardiovascular disease, cerebrovascular disease and limb amputation separately.

Median follow-up time was 9.34 months for all patients, 9.57 months for patients with AV fistulae,

<p>| Table 1. Population characteristics of patients with fistulas or grafts |
|----------------------------------------|-----------------|-----------------|-----------|</p>
<table>
<thead>
<tr>
<th>Fistula (%)</th>
<th>Graft (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;65 years</td>
<td>49.9</td>
<td>51.3</td>
</tr>
<tr>
<td>Females</td>
<td>33.3</td>
<td>61</td>
</tr>
<tr>
<td>Diabetes</td>
<td>24.5</td>
<td>33.8</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>16.7</td>
<td>10.4</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>11.2</td>
<td>6.5</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>4.5</td>
<td>2.6</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>2.2</td>
<td>1.3</td>
</tr>
<tr>
<td>iPTH &gt;400 pg/ml</td>
<td>27.1</td>
<td>41.8</td>
</tr>
<tr>
<td>ACE inhibitors or ARBs</td>
<td>33.2</td>
<td>32.5</td>
</tr>
<tr>
<td>rHuEPO therapy</td>
<td>75.0</td>
<td>81.3</td>
</tr>
</tbody>
</table>
10.34 months for patients with grafts and 5.67 months for patients with permanent catheters.

The Kaplan–Meier analysis revealed a cumulative survival for fistulae of 87 and 80% after 12 and 24 months, respectively. The results for graft survival were 74 and 56% after 12 and 24 months, respectively (Figure 1).

Median cumulative survival was ~5 months longer for AVFs than for grafts (25.38 months (24.68–26.09) vs 20.54 months (17.44–23.63)).

The RR of VA failure based on Cox analysis was 2.3 (95% CI: 1.37–3.86) times higher with grafts than with fistulae (P = 0.002).

The distribution of patients with grafts and fistulae in the four Hb groups is summarized in Table 2. For both types of VA, most patients fell in the group with Hb 10–12 g/dl. This Hb group was chosen as a reference for RR analysis.

The shortest VA cumulative survival was found in patients with Hb <10 g/dl (AVF 23.41 months; graft survival 14.3 months). The RR of AVF failure in those severely anaemic patients was 1.8 (2.86–1.13) times higher than in the patients with Hb between 10 and 12 g/dl (P = 0.013). Patients with Hb between 12 and 13 g/dl had an RR of AVF failure of 1.32 (0.84–2.08; P = 0.229), but patients with Hb >13 g/dl showed a lower RR of fistula failure, 0.77 (0.31–1.91; P = 0.585).

The RR of graft failure in severely anaemic patients (Hb <10 g/dl) was 1.61 (0.56–4.63) higher than in patients with Hb between 10 and 12 g/dl (P = 0.37). Patients with Hb between 12 and 13 g/dl had an RR of graft failure of 0.98 (0.28–1.68; P = 0.98; reference Hb, 10–12 g/dl).

With regards to the risk factors for VA failure apart from the Hb level, applying the Cox regression analysis (stratified by type of VA, Figure 2), the following major factors influencing VA survival were found: (i) treatment with ACE inhibitors or ARB was a protective factor for VA survival; it reduced the RR of VA failure by 31% (95% CI 0.49–0.98; P = 0.03); and (ii) older age, diabetes and high iPTH at admission were predictive of VA failure. The corresponding RR increased significantly by 32% (0.94–1.86; P = 0.11), 41% (0.98–2.02; P = 0.06) and 56% (1.10–2.21; P = 0.01), respectively.

Gender, vascular disease and rHuEPO therapy were not significantly related to VA survival.

Discussion

Any of the previously described advantages for dialysis patients of the complete correction of anaemia has to be balanced with the potential adverse effects of this practice. In the context of our study, we focused particularly on the possibility of an increased incidence of VA thrombosis. It is well known that complications

Table 2. Haemoglobin level during follow-up in patients with fistulae or grafts

<table>
<thead>
<tr>
<th>Hb level (g/dl)</th>
<th>No. of patients (%) with a fistula</th>
<th>No. of patients (%) with a graft</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb &lt;10 g/dl</td>
<td>180 (17.0%)</td>
<td>18 (24%)</td>
<td>NS</td>
</tr>
<tr>
<td>Hb 10–12 g/dl</td>
<td>647 (61.2%)</td>
<td>45 (60%)</td>
<td>NS</td>
</tr>
<tr>
<td>Hb 12–13 g/dl</td>
<td>170 (16.1%)</td>
<td>10 (13.3%)</td>
<td>NS</td>
</tr>
<tr>
<td>Hb &gt;13 g/dl</td>
<td>60 (5.7%)</td>
<td>2 (2.6%)</td>
<td>NS</td>
</tr>
<tr>
<td>Total</td>
<td>1057 (100%)</td>
<td>75 (100%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Fig. 1. Kaplan–Meier survival curve of different vascular accesses: fistulae, grafts and permanent catheters.
of VA are the primary causes of morbidity (hospitalizations) in HD patients. The matter is of utmost importance in clinical practice; and any practices that increase the incidence of these complications must be avoided. The potential association between VA thrombosis, higher Hb levels and rHuEPO therapy, however, remains controversial.

In our study, which evaluated an appropriately sized cohort of incident patients (1254), no significant differences were found in autologous fistula survival in patients with Hb levels between 10 and 12 g/dl and those with Hb between 12 and 13 g/dl or Hb > 13 g/dl; therefore, we assume that normalization of Hb levels was not an RR factor for fistula survival in our population. Moreover, it was shown that the severely anaemic patients (Hb <10 g/dl) were the group with a statistically significant shorter fistula survival; therefore, anaemia was a significant RR factor (P = 0.013) for fistula failure in our population.

Only 75 patients (5.9% of all our patients) had grafts as VA. Therefore, the statistical results in this small group have less capacity to allow reliable conclusions. Nevertheless, again the severely anaemic patients (Hb <10 g/dl) showed a higher RR of graft failure than those with an Hb between 10 and 12 g/dl or >12 g/dl.

Therefore, in our population, VA survival in non-anaemic patients was longer than in anaemic patients. This result is in conflict with a previous large sample, randomized clinical trial published by Besarab et al. in 1998 [7]. They concluded by recommending, in their ‘Normal Hematocrit Cardiac Trial’ (NHCT), against the normalization of Hb levels in HD patients. In this well-controlled clinical study, a stratified cohort of 1265 HD patients with clinically evident cardiac disease were randomized to achieve a maintenance haematocrit of either 42 ± 3 or 30 ± 3%. Increased access thrombosis was found in the cohort of patients randomized to achieve the higher haematocrit of 42% (39 vs 29%; P = 0.001). However, VA thrombosis was not associated with either the achieved haematocrit level or the dose of rHuEPO, making interpretation of these results difficult.

Such results conflicting with ours might be explained by the fact that most of the patients in the Besarab study had grafts, whereas in our study most patients had AVFs.

Another relevant difference between the Besarab study and ours is the design of the study. The former is an interventional trial, where patients are randomly forced to reach a certain Hb level. Our study, however, is an epidemiological evaluation, where the target Hb is established by the European Best Practice Guidelines [1], but the physicians are not forced to normalize Hb in patients resistant to correction. On the other hand, our finding that severe anaemia was associated with a higher risk of VA failure can be explained by the association of the anaemic state with inflammatory states and the presence of co-morbidities in many HD patients. This hypothesis is in keeping with the findings of a study by Miller et al. [10], who found a shorter graft survival in patients with hypoalbuminaemia compared with patients with normal serum albumin levels. Patients with inflammatory states would have EPO resistance and, thus, lower Hb levels. Moreover, their inflammatory state would increase the likelihood of access failure. These two opposing effects would be obscured in a randomized study, given that no correlation between patient Hb and the likelihood of access thrombosis was observed. Accordingly, in another randomized controlled trial investigating the effect of Hb levels on left ventricular hypertrophy, Foley et al. [11] found no difference in the incidence of arteriovenous access thrombosis in patients with low Hb (9.5–10.5 g/dl) compared with individuals with normal levels (13.0–14.0 g/dl).

Autologous fistulae are recommended as the first-choice VA for HD patients [2], in preference to prosthetic grafts, because the former have better patency rates and less need for corrective interventions, and are, therefore, associated with significantly lower morbidity and costs. Our results also strongly support the advantages of autologous fistulae vs grafts as VA for HD: our study showed that the RR of graft failure was 2.3 times higher (P = 0.002) than autologous fistula failure.
and fistula survival was significantly longer than graft survival.

Apart from anaemia correction, we found other factors that could be influencing VA survival: diabetes and hyperparathyroidism were associated with a higher risk of VA failure; treatment with an ACE inhibitor or ARB was associated with longer VA survival. In addition to the classic atherogenic risk factors (diabetes and age), iPTH has recently been suggested as a potential cause of vascular disease. Grandaliano et al. [12] investigated the relationship between fistula dysfunction and mean plasma iPTH in 36 patients. They found that patients with fistula failure had significantly higher mean plasma iPTH. The increased RR of access failure that we found in patients with baseline iPTH >400 pg/ml might be related to uncontrolled hyperparathyroidism during the pre-dialysis period and the consequent vascular damage.

The protective effect of ACE inhibitors has already been described in the literature. Saran et al. [13] found a significant reduction of the risk of fistula failure with the use of ACE inhibitors (RR: 0.56; \( P = 0.010 \)) when they investigated 90 fistulae in a prospective, observational study (DOPPS: Dialysis Outcomes and Practice Pattern Study). In a series of 121 grafts, Gradzki et al. [14] reported a substantially lower risk of graft failure in patients who used ACE inhibitors, compared with those who did not (RR: 0.32; \( P = 0.003 \)). Our findings are consistent with these results; consistent also in terms of the magnitude of the decrease of the RR, calculated by us to be \( \sim 31\% \).

Several mechanisms have been proposed for this protective effect: inhibition of intimal hyperplasia, vascular smooth muscle cell proliferation and migration, and extracellular matrix deposition. In addition, an ACE inhibitor or ARB may improve blood flow by increasing cardiac output associated with afterload reduction.

Conclusions

In our population, anaemia (Hb <10 g/dl) was associated with VA failure. No significant differences were found in fistula and graft survival between patients with nearly normal Hb and those with Hb between 10 and 12 g/dl.

Our study showed that HD patients should benefit from anaemia correction without incurring any increased risk of VA failure.

A significantly protective effect of ACE inhibitors or ARBs on VA survival was detected. In contrast, older age (>65 years), diabetes and high baseline iPTH were predictive risk factors for access failure in our study. ACE inhibitors, already recommended for their protective effects on the heart, should also be considered for their potential beneficial impact on VA survival, especially in older diabetic patients with high iPTH levels, because of their risk of VA failure. Moreover, in those patients, the VA has to be monitored carefully.

Conflict of interest statement. None declared.