Prediction of time-averaged concentration of haemoglobin in haemodialysis patients

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Abstract

Background. Haemoglobin (Hb) concentration is not stable in most haemodialysis patients due to ultrafiltration-induced haemoconcentration. Pre-dialysis Hb concentrations might therefore significantly deviate from the time-averaged concentration (Hb-tac) which is more likely to represent the patients 'true' Hb. This study was performed to quantify these differences in our chronic haemodialysis population and to develop a formula for prediction of Hb-tac.

Methods. In 55 stable patients, serial blood samples were taken over a period of 2 weeks before and immediately after each haemodialysis as well as 30 min post-haemodialysis to account for post-dialytic fluid rebound. Hb-tac was calculated for every patient from the area under the time-dependent Hb curve. We compared the differences between Hb-tac and pre-dialysis Hb (Hb-pre) and various prediction formulae for Hb-tac generated by multiple linear regression analysis which included Hb-pre and post-dialysis Hb (Hb-post) and/or ultrafiltration rate (UFR).

Results. Mean Hb-pre after the long dialysis interval was significantly lower than after the short interval (11.47 vs 11.85 g/dl, P < 0.0001), both underestimating mean Hb-tac (11.97 g/dl). More interestingly, Hb-pre after the long interval deviated >0.5 g/dl from Hb-tac in 50% of measurements. After the short interval, 20% still lay outside this tolerance range. The best formula to predict Hb-tac was Hb-pre/C20.5 + Hb-post/C20.38 + 1.28 (6% outside ± 0.5 g/dl). Hb-pre + (Hb-post – Hb-pre)/3 may be used for quick estimation of Hb-tac.

Conclusions. Hb-tac can be predicted from pre- and post-dialysis blood samples after the short interval, using a simple new formula. Because Hb-tac more reliably reflects a 'true' Hb level of haemodialysis patients, it represents a potentially useful tool for future scientific and clinical work.

Keywords: haemodialysis; haemoglobin; post-dialysis; prediction; target; time averaged

Introduction

Correction of anaemia in haemodialysis (HD) patients with recombinant erythropoietin and i.v. iron is well established and has great impact on the patients well-being as well as on treatment costs [1–7]. Control of haemoglobin (Hb) in clinical practice as well as in virtually all studies dealing with the effects of anaemia correction in this population is usually based on pre-dialysis blood sampling [6–9]. Also the guidelines for anaemia management published in the last few years by several renal associations refer to pre-dialysis values when recommending Hb target values [10,11]. However, Hb concentration is variable in HD patients. Pre-dialysis values vary with the time of blood sampling, e.g. they are lower after the long than after the short interdialytic interval [12,13]. Furthermore, pre- and post-dialysis Hb concentrations may differ by up to 25% or 3.5 g/dl [13–15], depending on ultrafiltration, hydration status and other effects, and they are subject to a post-dialytic rebound. This results in a saw-toothed pattern of Hb concentrations when seen over a whole week (for an example, see Figure 1).

Time averaging is a common approach to characterize a variable with marked time-dependent changes. Such a time-averaged Hb concentration (Hb-tac) could be considered close to the 'true functional' Hb as claimed by some authors [11,16]. In patients without intradialytic haemoconcentration, pre-dialysis Hb
(Hb-pre) may be regarded as a good estimate for the patients ‘true’ Hb and should be comparable with the Hb of individuals not on HD. In contrast, in patients with a high ultrafiltration rate (UFR), haemoconcentration causes a considerable increase in post-dialytic Hb (Hb-post). Thus, Hb-pre will significantly underestimate the Hb-tac in these patients. Furthermore, with increasing efforts to increase target Hb concentrations [4,6,8,9], it is more likely that Hb-post will reach dangerous levels in a growing number of HD patients [17]. Although these problems are raised from time to time [13,15–17], studies aimed at solving this dilemma do not exist.

It was the intention of this study to first evaluate the magnitude of Hb variations in our dialysis population as encountered under daily conditions. The second goal was to determine Hb-tac and to compare this value with pre-dialysis levels. Finally, we wanted to develop a formula for predicting Hb-tac from easily accessible parameters for potential routine use.

Subjects and methods

Patients

Patients were selected from our chronic out-patient HD programme consisting of 70 patients. Only patients who had been on HD for at least 3 months with three sessions per week were selected. Patients who had a significant intercurrent illness or were clinically unstable as judged by the attending physician were excluded. Also patients with unstable Hb during the 2-week study period were not evaluated. This was defined as a difference in mid-week Hb-pre of > 1 g/dl during the study period or the need for red blood cell transfusions, and was the case in two patients. All included patients were on dry weight as clinically assessed. In a subset of 12 patients, this was confirmed by measurement of vena cava diameter indices [18].

Fifty-five stable patients were recruited (21 women, 34 men; 54 Caucasians, one black; mean age 58.9 ± 16.9 years; 4.2 ± 3.2 years on HD; mean body weight 68.8 ± 11.1 kg). Causes of chronic renal failure were hypertension (n = 11), glomerulonephritis (n = 7), diabetes mellitus (n = 6), others (n = 14) and undetermined (n = 17).

Treatment

Treatment was performed as routinely prescribed; however, to allow for a rebound sample taken 30 min after the end of HD, treatment time was reduced by that amount in those who requested it. Treatments were performed on AK 200 machines (Gambro AB, Stockholm, Sweden) using synthetic low-flux dialysers for HD and synthetic high-flux dialysers for haemodiafiltration (HDF) supplied by various manufacturers. Following the routine procedures for connecting and disconnecting the blood lines, ~300 ml of saline were infused mainly at the end of each HD. The study was approved by the local Ethics Committee, and all patients provided written informed consent.

Blood chemistries

Blood samples were drawn before dialysis from the arterial puncture site (Hb-pre), at the end of dialysis under low flow conditions from the arterial blood line (Hb-post), and 30 min after the end of dialysis (Hb-reb) for six consecutive HD sessions over a period of 2 weeks. We considered 30 min as a reasonable time span for allowing extravascular fluid to rebound from the interstitial space [19,20]. A final Hb-pre was drawn at the beginning of the third week. Hb was analysed photometrically and haematocrit derived indirectly by an automated cell counter (Sysmex™ XE 2100, Toa Medical Electronics, Kobe, Japan). The coefficient of variation in our laboratory is 1.1% for Hb, and 1.5% for haematocrit. Only Hb is presented in the results, because it seems to be more comparable between laboratories [21] and Hb concentrations are more steady in vitro over time [22] and therefore should be used in preference to haematocrit to manage anaemia [10,11].

Analysis

For every individual patient, a Hb curve as a function of time over the 2-week study period was constructed, connecting Hb-pre, Hb-post and Hb-reb by straight lines (compare Figure 1). Hb-tac was calculated from the area under this curve divided by the duration of the observation. When data were incomplete for the whole 2-week period, only one complete week (e.g. Monday to Monday) was evaluated.

The capability of Hb-pre sampled on different days to predict Hb-tac was compared with respect to the residual standard deviation (RSD). RSD is defined as the standard deviation of the differences between predicted and observed values of Hb-tac (‘residuals’). The percentage of residuals exceeding ±0.5 g/dl was used as an additional performance criterion. This value of 0.5 g/dl was chosen as the relevant discrepancy since most of the established guidelines use this range to indicate Hb targets (e.g. NKF-K/DOQI: 11.5 ± 0.5 g/dl) [10].

In a second step, formulae for prediction of Hb-tac were obtained by linear regression analysis using Hb-pre, Hb-post, UFR or subsets of these. For these calculations, we only used values after the short interval. We excluded the rebound sample Hb-reb for prediction modelling because for possible routine use it would be impracticable to draw blood samples 30 min after the end of HD. Hb-pre and Hb-post used for prediction also contribute to Hb-tac. This can be neglected for Hb-post but yields too optimistic results for formulae containing Hb-pre. Therefore, for the calculation of residuals
for each Hb-pre, an independent Hb-tac was also determined by replacing this particular Hb-pre with the Hb-pre from the successive week for samples taken on Mondays, and switching Hb-pre concentrations from Wednesdays and Fridays within the same week. The Tuesday, Thursday and Saturday schedule was handled in the same way. In the following text, Mondays or Tuesdays (after the long dialysis interval) are also termed day 1, Wednesdays or Thursdays day 3, and Fridays or Saturdays day 5, respectively.

The percentage of dialysis-induced haemoconcentration (HC%) was calculated by the formula: 

$$\text{HC\%} = 100 - \left( \frac{\text{Hb-pre}}{\text{Hb-post}} \right) \times 100.$$ 

**Statistics**

Unless otherwise specified, data are expressed as mean ± SD. Mean Hb concentrations were compared by paired t-tests using only the measurements of the first week in order to achieve statistical independence between pairs. P-values were multiplied by the number of comparisons to maintain the significance level (Bonferroni correction). A P < 0.05 was considered statistically significant.

Excel™ (Microsoft, Seattle, WA), SPSS™ (Chicago, IL) and SASS™ (Cary, NC) were used for calculations.

**Results**

Complete data over the whole 2 week study period were obtained in 41 patients; in 14 patients only 1 week could be assessed. Mean dialysis time was 3.75 ± 0.34 h (median 3.5), and ultrafiltration volume was 2.4 ± 1.0 l, corresponding to a UFR of 0.64 ± 0.27 l/h. Dialysate sodium was 137 ± 3 mmol/l (median 138), bicarbonate 31 ± 2 mmol/l (median 30), potassium 1.9 ± 1.1 mmol/l (median 2.0) and glucose 1 g/l in all patients. Machine blood flow was 296 ± 42 ml/min (median 300), and dialysate flow 500 ml/min in HD (78% of patients) and 700 ml/min in HDF.

The Hb concentrations of the evaluated 288 HD sessions are presented in Table 1 and Figure 1. Mean Hb-pre after the long interval was significantly lower than after the short interval (11.47 vs 11.85 g/dl, P < 0.0001), while there was no significant difference between day 3 and day 5 mean Hb-pre levels (11.80 vs 11.90 g/dl, P = NS). Mean treatment-induced haemoconcentration was 6.7% after the long and 5.1% after the short interval (P < 0.05). Mean Hb-tac (11.97 g/dl) was significantly higher than mean Hb-pre at either day (P < 0.001).

The differences of each individual Hb-pre value from the patients’ Hb-tac plotted against UFR are shown in Figure 2. As expected, there was increasing

Table 1. Mean haemoglobin concentrations (g/dl)a

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 3</th>
<th>Day 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb-pre</td>
<td>11.47 ± 1.09b</td>
<td>11.80 ± 1.12</td>
<td>11.90 ± 1.16</td>
</tr>
<tr>
<td>Hb-post</td>
<td>12.30 ± 1.47</td>
<td>12.45 ± 1.50</td>
<td>12.52 ± 1.43</td>
</tr>
<tr>
<td>Hb-reb</td>
<td>12.04 ± 1.33c</td>
<td>12.26 ± 1.35</td>
<td>12.25 ± 1.29</td>
</tr>
<tr>
<td>Hb-tac</td>
<td>11.97 ± 1.11d</td>
<td>11.97 ± 1.11d</td>
<td>11.97 ± 1.11d</td>
</tr>
</tbody>
</table>

aMean values are based on all data. Only one pair of values per patient was used in the t-test.
bP < 0.0001 with respect to Hb-pre at days 3 and 5.
cP < 0.01 with respect to Hb-reb at days 3 and 5.
dP < 0.001 with respect to Hb-pre at days 1, 3 and 5.

![Fig. 2. Residuals after prediction of time-averaged haemoglobin (Hb-tac) by pre-dialysis haemoglobin (Hb-pre): Hb-tac minus Hb-pre, n=288. Residual standard deviation (RSD) is 0.51 g/dl for the whole group; it is larger after the long interval (0.66 g/dl) than after the short interval (0.42 g/dl). Bold lines mark the ±0.5 g/dl tolerance range. At day 1, 50% of the residuals lay outside this range compared with 20% at days 3 and 5 (P < 0.0001).](https://academic.oup.com/ndt/article-abstract/18/10/2082/1807744)
underestimation of Hb-tac at higher UFR: the linear regression line for Hb-tac – Hb-pre was $UFR \times 0.61 - 0.15$ ($P < 0.0001$, $r^2 = 0.11$). The quality when using Hb-pre to predict Hb-tac is shown in Table 2. Overall, 30% (86/288) of Hb-pre deviated >0.5 g/dl from Hb-tac, corresponding to an RSD of 0.51 g/dl, with a maximum difference of 2.5 g/dl. This proportion differed significantly between samples drawn after the long or the short HD interval: 50% (48/96) at day 1 vs 20% (38/192) at days 3 or 5 ($P < 0.0001$). As prediction of Hb-pre was better after the short interval, we decided to include only these days in further analysis.

Table 2 shows the results of various linear regression models. Hb-tac was best predicted by $Hb-pre \times 0.5 + Hb-post \times 0.38 + 1.28$ (RSD = 0.28). The residuals after prediction with this formula are plotted in Figure 3. Only 6% (11/192) fell outside the mentioned ±0.5 g/dl range. The benefit is even more pronounced if only HDs with UFR of 0.5 l/h or above are viewed: in only 2.8% (3/108) did the predicted Hb differ >0.5 g/dl from Hb-tac, vs 21% (23/108) if Hb-pre was used. Incorporating UFR into the formula showed no advantage.

For the potential use as a bedside estimation of Hb-tac, simplified formulae were tested (Table 2). $Hb-pre + (Hb-post - Hb-pre)/3$ is a better approach than using the mean of Hb-pre and Hb-post (RSD 0.32 vs 0.37).

**Discussion**

This study attempts to determine Hb-tac in a cohort of stable HD patients by including post-dialytic fluid rebound in the calculations, and describes its discrepancy to pre-dialysis values. A formula is presented to predict Hb-tac from pre- and post-dialysis Hb concentrations.

The mean Hb-pre of our study population was within the recommended targets [10,11] and was significantly lower after the long interval than after the short interval, an expected effect [12,13] of more pronounced overhydration at the beginning of the week (Table 1). We observed a dialysis-induced haemoconcentration of 5–7%, somewhat smaller than reported in other studies, where mean intradialytic variations of haematocrit were in the range of 10% [13,14,23].

Our data confirm that in most HD patients, unlike in the general population or patients on peritoneal
dialysis, Hb concentrations show significant short-lasting changes. Depending on sampling time or on theoretical considerations, various Hb values can be attributed to the same patient during 1 week. Which one should be chosen? Our goal was to derive a representative value for the Hb concentration in our HD patients which should be more comparable between them as well as with people not on HD. This might be important for research dealing with the effects of different Hb targets on physical or mental abilities, on morbidity and on mortality. Lack of comparability of individual Hb levels could play a role in the partially disappointing results of some studies dealing with the normalization of Hb [7,8]. Consideration of HD-induced haemoconcentration may also be prudent for the individual patient in our daily routine as we know that patients might live the major part of the time with Hb levels well above those suggested in predialysis samples [15,16]. We think that Hb-tac can meet the mentioned demands. We want to acknowledge that there exist alternative approaches to overcome the problem of Hb variability in patients with renal anemia. Clyne et al. used the concept of ‘total haemoglobin’ (the body content of haemoglobin in grams), a marker independent of the actual hydration status, and they could show a strong relationship to physical exercise capacity in these patients [24].

The simplest way to approximate Hb-tac, as it is already more or less prevalent in the nephrological community, is the use of Hb-pre after the short interval only: for the whole group, this gives an acceptable estimate for mean Hb-tac. Obviously, individual deviations, which may be substantial for any particular person, will not be detected. We could show that this approach does not provide satisfactory results in at least 20% of our patients.

Using our formula including a post-dialytic sample after the short interval lowered false estimations of Hb-tac by two-thirds to 6%. If applied in the high UFR group (>0.5l/h), where we expect the largest differences between Hb-pre and Hb-post, the Hb-tac will be correctly predicted within the specified limits in 35 out of 36 patients.

A limitation of our study is that Hb-tac cannot be measured accurately, since portable devices analogous to continuous blood pressure monitoring do not exist. The Hb-tac we used as reference is a simplification: in our model, we assumed that there is a constant decrease or increase between times of blood sampling. This is justifiable during dialysis and rebound as deviations from linearity are negligible in their contribution to Hb-tac. This may not apply for the much longer interdialytic period. We have to suppose that a number of patients did not follow a linear intradialytic decrease, but to individualize this period accurately in our patients by obtaining multiple blood samples on interdialytic days was not practicable. Although one study showed an almost linear decline of haematocrit during the interdialytic period [16], recent data [13,15] suggested a slower re-equilibration during the first 24 h after HD. If this was really the case, Hb-tac would be even higher than calculated in our model and further increase its discrepancy to Hb-pre. For obvious reasons, the determination of Hb-tac by repeated blood sampling over a longer period of time is impracticable for routine use. In contrast, the formulae proposed herein to estimate Hb-tac make use of two easily accessible Hb measurements only: Hb-pre and Hb-post. The required post-dialytic blood count can be collected together with the urea sample for the monthly Kt/V, and Hb-tac can then be calculated automatically in the laboratory. Furthermore, Hb-post may serve as a safety measure since in the immediate post-dialytic period Hb can reach critically high levels [17], especially in patients in whom ‘normalization’ of Hb is the goal. For quick estimation of Hb-tac, one can use our simplified formula Hb-pre plus a third of the difference between that and Hb-post.

For patients without haemoconcentration or treatment-induced haemodilution, it might not be required to use a correction as, in those cases, ultrafiltration-induced haemoconcentration, which is the basis of our model, obviously plays a minor role.

The formula presented in this study is valid for populations with comparable dialysis modes, patient characteristics and mean Hb levels. It should only be used in stable patients on dry weight, as chronic hyperhydration would obviously influence Hb-tac without any change in the patients ‘total’ Hb [24]. Whether this formula also applies to other treatment modes, especially with regard to higher ultrafiltration volumes and UFRs, remains to be investigated, although our proposed formula for prediction of Hb-tac was even more accurate at higher UFRs.

How could the determination of Hb-tac influence our clinical dosing of erythropoietin? Optimal target values for Hb-tac can certainly not be derived from this study, but they are likely to be higher than the currently recommended values for Hb-pre. Future outcome studies that use Hb-tac as a steering parameter could provide a definite answer to this question. Nonetheless, Hb-tac can be used to define Hb targets in HD patients independent of varying pre-dialysis hydration states. As no data exist as to whether knowledge of Hb-tac justifies an additional blood sample, we suggest making use of this marker primarily as a scientific tool.

In conclusion, the time-averaged concentration of haemoglobin is a new and representative marker for anaemia management in HD patients and can be predicted from pre- and post-dialysis blood samples after the short interval using a simple new formula. Because Hb-tac more reliably reflects the ‘true’ Hb level of these patients, it is a potentially useful tool for future scientific and clinical work.

Conflict of interest statement. None declared.

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2087

Time-averaged Hb concentration in HD patients

Received for publication: 5.9.02
Accepted in revised form: 12.5.03


