Protocol adherence and the ability to achieve target haemoglobin levels in haemodialysis patients

Kevin Chan\(^1\), John Moran\(^2\), Mark Hlatky\(^3\) and Richard Lafayette\(^1\)

\(^1\)Department of Nephrology, \(^2\)Satellite Healthcare, Inc, Mountain View, CA and \(^3\)Health Research and Policy, Stanford University School of Medicine, Stanford, CA, USA

Correspondence and offprint requests to: Kevin Chan; E-mail: Kevinchan9999@hotmail.com

**Abstract**

**Background.** Anemia management remains complicated in patients with endstage renal disease on hemodialysis. We wished to evaluate the effect of protocol adherence to EPO and intravenous iron dosing on achieving the desired range of hemoglobin levels.

**Methods.** A cohort of hemodialysis patients was studied to evaluate the rate of adherence to EPO and iron dosing protocols over a 5 month period. A database was completed to evaluate all known comorbidities, demographic factors, and facility issues that might affect hemoglobin levels. A logistic regression model was employed to evaluate the effect of adherence to the anemia protocols on the probability of achieving a hemoglobin level below, within or above the targeted range of 11–12.5 g/dl.

**Results.** Among 2114 patients, we found that adherence to both the EPO and iron dosing protocol resulted in the greatest probability of achieving the target hemoglobin range (56 ± 5% in anemia protocol adherent patients versus 42 ± 7% in non adherent patients). This was predominantly due to a lowered risk of having above target hemoglobin levels rather than below. The use of the anemia protocols was associated with lower rates of hospitalization (9 ± 0.7 visits/100 months in adherent group vs 15 ± 2 in non adherent group) and lower utilization of both EPO and intravenous iron. Furthermore, patients in the adherent groups had less variability of their hemoglobin levels month by month, at least as judged by standard deviation.

**Conclusion.** Adherence to anemia protocols, as practiced in the dialysis units included in this cohort, may improve hemodialysis patients’ ability to achieve target hemoglobin levels, and by avoiding above target hemoglobin values, lower drug utilization and reduce variability of hemoglobin levels.

**Keywords:** anaemia management; ESRD; processes of care

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Introduction

Anaemia in the dialysis population remains prevalent [1], its treatment is costly [2] and it has been associated with significant morbidity [3, 4] and mortality [5] when inappropriately treated. Recent studies have suggested the importance of maintaining haemoglobin levels within a tight range to limit complications of anaemia or its treatment [6]. However, anaemia management in the end-stage renal disease (ESRD) population continues to be suboptimal in the United States as many patients do not achieve or overshoot the target haemoglobin range [7]. Despite the introduction of new therapy [8], publication of new research [9, 10] and initiation of quality improvement programs [11, 12], the clinical effectiveness of anaemia management has not improved over time [13]. Currently, large and unexplainable differences in anaemia management performance continue to exist at the individual, facility [14, 15] and regional [16] level, despite the availability of published clinical practice guidelines for the use of erythropoietic-stimulating agents and intravenous iron [17, 18]. Although patient factors [19] have been shown to affect success in anaemia management, considerably less research has investigated the role of processes of care.

We previously reported that the implementation of a uniform EPO and IV iron titration protocol was associated with better anaemia outcomes in a chain of dialysis facilities in Northern California [14]. That study examined effects on a facility-wise level and examined whether patients were assigned to an anaemia treatment protocol or not. While enrolling patients to an anaemia management protocol was shown to be quite common, it remains unproven whether the beneficial effects of a ‘one size fits all’ protocol can directly be attributed to the algorithm itself or is a phenomenon of patient selection. To answer this question from the patients’ perspective, we translated the existing 11-page anaemia protocol into a computer program to assimilate lab values and drug orders to generate protocol adherent EPO and IV orders for comparison to actual administered doses of the medications. This allowed us to evaluate not only if the protocol was ordered, but whether the patient ended up receiving the protocol dose without it being changed in error or by a doctor’s or nurse’s override. We hypothesized that following a pre-written protocol correctly would increase the achievement of a pre-specified haemoglobin interval, decrease drug utilization and limit swings in haemoglobin values attributable to either too large or too frequent adjustments in dosing of iron and EPO.

Subjects and methods

Sample

We constructed a cohort of prevalent haemodialysis patients among individuals receiving maintenance haemodialysis at all units operated by Satellite Healthcare, Inc. (Mountain View, CA, USA) that was accredited during the time period of the study. Individuals new to dialysis (<=31 days) were excluded. The final cohort consisted of 1639 patients.

Primary outcome

The primary outcome was a categorical variable based on the haemoglobin concentration either below, above or within the target range of 11–12.5 g/dL. This interval was the recommended target by the Centers for Medicare and Medicaid Services (CMS) at the time of the study [20, 21] and was the satellite dialysis goal during the study period. The second outcome was EPO and iron utilization, as well as intra- and inter-patient haemoglobin standard deviation which served as surrogates for haemoglobin cycling, a proposed quality-of-care metric which has been associated with mortality in ESRD patients [22].

Anaemia management protocol

All ‘anaemia managers’ (nurses responsible for tracking haemoglobin concentrations and coordinating orders for EPO and iron therapy) at the 15 participating dialysis units were instructed to follow the same standardized anaemia management protocol using epoetin alfa (EPOGEN®; Amgen, Thousand Oaks, CA, USA) and iron sucrose (Venofer®; American Regent, Shirley, NY, USA) to a target haemoglobin interval between 11 and 12.5 g/dL. Nurses are instructed to review pertinent laboratory values and titrate EPO and iron doses by following the protocol on the third Monday and Tuesday of every month. The protocol was developed at Satellite Healthcare based on the current literature, including clinical practice guidelines [12] and manufacturing dosing recommendations. The implemented protocol targeted a haemoglobin level between 11 and 12.5 g/dL, transferrin saturation between 25% and 50% and ferritin between 200 and 800 ng/mL. Patients with iron levels below target by either iron saturation or ferritin would receive 500–1000 mg of IV iron over five sessions and those within target would receive 100–200 mg of maintenance iron every other week. All iron products were held if the ferritin exceeded 800 ng/mL. EPO doses could be changed up to 25% and titration was based on a patient’s haemoglobin trend over the past 30–90 days. The EPO dose would be abruptly dropped to 500 units if the current haemoglobin level exceeded 14 g/dL and restarted with a 25% dose reduction once the level fell below 12.5 g/dL. The protocol outlined precise titration instructions for EPO and iron dosing based on a patient’s iron saturation and ferritin, haemoglobin and haemoglobin trend over the previous 3 months.

Adherence to protocols

We transcribed the current anaemia management protocol into an SAS computer program. In conjunction with patient laboratory and electronic order data, we used this program to determine whether a patient was adherent to the recommended dosage of EPO and iron for each month a patient was enrolled in the study. Adherence to the EPO protocol was achieved if the absolute percent difference between the administered and recommended dose was within 10%. Adherence to the iron protocol was achieved when the total amount of iron administered within a 1-month period was within the predetermined dosing range for the patient’s individual saturation and ferritin levels. Percent deviation from the protocol was defined as the percentage difference between the administered and recommended dose. Non-adherence occurred by a nurse or physician intentionally changing the dose or a mistake in the calculated dose.

Statistical analysis

We used multinomial logistic regression to determine the effect of adherence to EPO and/or iron dosing protocols on achieving the target haemoglobin interval (11–12.5 g/dL) at the end of a month-long anaemia management cycle. Adherence was modelled as a categorical variable (adherence to EPO only, iron only or both EPO and iron dosing; reference was adherence to neither). The model included age, adjustment for facility (14 categorical variables), initial haemoglobin level, parathyroid hormone, Kt/V, C-reactive protein, diabetes (yes versus no), reuse (number of dialyser changes per month) as a potential measure of clotting or blood loss in the filter, hospitalizations and sex, covariates that were found to influence targeted anaemia management as reported in a previous cross-sectional analysis on the same patient population [14]. Correction for correlations of observations within each patient over time was done with a robust sandwich estimator of variance [23].
We used four separate linear regression models, with inclusion of the same covariates mentioned above, to estimate EPO utilization, iron utilization and the standard deviation of haemoglobin by adherence to protocol. The standard deviation of the modelled end of month haemoglobin under different EPO and iron adherence scenarios was used to calculate inter-patient variability. To calculate intra-patient variability, the haemoglobin standard deviation and adherence rate were calculated for each patient (i.e. for each patient, the rate was number of months the patient was adherent divided by the number of months the patient was enrolled in the study) who was enrolled in the study for at least 2 months (i.e. at least two haemoglobin readings). We then used linear models to estimate the patient level standard deviation (independent variable) as a function of adherence rate and baseline covariates (dependent variables).

Finally, we performed two sensitivity analyses to validate our primary conclusion. To account for the effect of missed treatments and comorbidity not accounted for in the hospitalization and C-reactive protein, we repeated the primary analysis censoring patients once they were hospitalized. We also performed our primary analysis stratified by the beginning of month haemoglobin level to see whether the protocol could successfully bring haemoglobin to the target, regardless of where their haemoglobin started. Multivariate analysis determined that patients adherent to the EPO and/or iron management protocol (versus non-adherent) were less likely to overshoot the upper haemoglobin target 12.5 g/dL. Adherence to the EPO protocol was 53% and adherence to the iron protocol was 77%.

Table 1 presents the patient characteristics of our study population based on adherence to either or both of the EPO or iron protocols.

Univariate analyses demonstrated that adherence to the EPO and/or iron protocols was associated with lower mean haemoglobin levels and a higher likelihood of achieving the targeted haemoglobin level (Table 2). Table 2 also demonstrates the mean deviation from the protocol for patients who were treated with different dosing. For those patients treated off the EPO protocol, 63% received higher EPO doses and 37% lower. For patients treated off the iron protocol, 30% received more iron and 70% received less than would have been given on protocol. Adherent patients were found to be significantly less likely to be hospitalized within the month.

Multivariate analysis determined that patients adherent to the EPO and/or iron management protocol (versus non-adherent) were less likely to overshoot the upper haemoglobin target 12.5 g/dL. In contrast, protocol adherence (versus non-adherence) did not play a significant role in preventing the haemoglobin level from falling below 11 g/dL (Table 3). The adjusted probability of achieving the target haemoglobin level was 66% when adherent to both EPO and iron protocols, 64% when adherent to EPO only, 57% when adherent to iron only and 51% when non-adherent to both protocols (Figure 1).

### Results

Patients who were receiving dialysis from July 2005 to November 2005 were initially examined for study eligibility. After exclusion of missing data (211 patients) and patients new to dialysis (264 patients), the final cohort included 1639 (78%) patients (providing 6455 patient months of data). The mean haemoglobin concentration was 12.1 g/dL (standard deviation 1.2 g/dL). A total of 14.9% of the patients were below, 32.8% were above and 52.3% were within the target interval of 11–12.5 g/dL. Adherence to the EPO protocol was 53% and adherence to the iron protocol was 77%.
Table 3. Association between adherence to protocol and success in anaemia management

<table>
<thead>
<tr>
<th></th>
<th>Odds of below target</th>
<th>95% CI</th>
<th>Odds of above target</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adherence to protocol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EPO and iron</td>
<td>0.84</td>
<td>0.63–1.13</td>
<td>0.48</td>
<td>0.39–0.59</td>
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<tr>
<td>EPO only</td>
<td>0.84</td>
<td>0.59–1.19</td>
<td>0.53</td>
<td>0.41–0.68</td>
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<tr>
<td>Iron only</td>
<td>1.11</td>
<td>0.84–1.46</td>
<td>0.70</td>
<td>0.57–0.85</td>
</tr>
<tr>
<td>None</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Age (years)</td>
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<td>0.98–1.00</td>
<td>1.00</td>
<td>0.99–1.01</td>
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<tr>
<td>Kt/V</td>
<td>1.07</td>
<td>0.90–1.27</td>
<td>0.83</td>
<td>0.72–0.94</td>
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<tr>
<td>Initial hgb (g/dL)</td>
<td>0.46</td>
<td>0.41–0.51</td>
<td>2.56</td>
<td>2.36–2.75</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>1.006</td>
<td>1.002–1.01</td>
<td>1.00</td>
<td>0.99–1.004</td>
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<td>PTH (100 pg/mL)</td>
<td>1.02</td>
<td>0.99–1.04</td>
<td>0.99</td>
<td>0.97–1.01</td>
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<td>Gender (female)</td>
<td>1.05</td>
<td>0.89–1.26</td>
<td>1.00</td>
<td>0.88–1.14</td>
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<tr>
<td>Reuse (changes per month)</td>
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<td>0.98–1.03</td>
<td>1.02</td>
<td>0.99–1.04</td>
</tr>
<tr>
<td>Diabetic</td>
<td>1.02</td>
<td>0.85–1.22</td>
<td>0.96</td>
<td>0.84–1.09</td>
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<tr>
<td>Hospitalizations (visits per month)</td>
<td>2.48</td>
<td>2.03–3.06</td>
<td>0.58</td>
<td>0.44–0.74</td>
</tr>
<tr>
<td>Facility (15 sites)</td>
<td>0.90–3.03</td>
<td></td>
<td>0.65–1.02</td>
<td></td>
</tr>
</tbody>
</table>

PTH: parathyroid hormone; hgb: haemoglobin.

Linear regression modelling showed that adherence to the anaemia management protocol was associated with significantly lower utilization of anaemia medications while maintaining more patients in the target range (Figures 2 and 3). The best results (lower drug utilization and more patients in the target range) were obtained when both EPO and iron were dosed per protocol.

Patients who adhered to the EPO ($P < 0.0001$) and iron ($P < 0.0001$) protocol had less scatter of haemoglobin values when compared to non-adherence (inter-patient comparison), which translates to a decreased number of patients falling outside the targeted interval (Figure 4).

Adherence to EPO ($P = 0.001$) and iron ($P < 0.0001$) protocol was also statistically associated with less intra-patient month-to-month haemoglobin variability when compared to non-adherence (Figure 5).

Results after censoring patients after hospitalization were statistically no different than the primary findings (Table 4). Analysis by a patient’s initial haemoglobin demonstrated most patients benefited from protocol-based anaemia management with statistical significance achieved in preventing high haemoglobin levels when patients started the anaemia management cycle with haemoglobin levels above or within the target range.

Discussion

This retrospective study suggests that adherence to an anaemia management protocol can bring patients to a predetermined target haemoglobin level more frequently than off-protocol dosing of EPO and iron. Adherence to EPO and iron protocols is also associated with decreased drug utilization and haemoglobin variability, which has been postulated to cause excess mortality in the ESRD population [13,22].

Anaemia management in haemodialysis patients has come under close scrutiny with calls to achieve target haemoglobin levels and optimize resource utilization [2, 24]. Recent studies have suggested a narrow range...
Fig. 3. Adjusted iron utilization by adherence to standardized dosing guidelines. A total of 95% confidence interval indicated by error bars.

Fig. 4. Adjusted inter-patient sampling distributions for haemoglobin by adherence to anaemia management protocol. *p < 0.0001 relative to other haemoglobin sampling distributions. Decreased haemoglobin variability is noted between different levels of adherence. The non-adherent group showed the most variability which resulted in more patients falling outside the targeted interval. The mean and standard deviation of hemoglobin values is shown for each group in parenthesis.

Fig. 5. Adjusted intra-patient sampling distributions for haemoglobin by adherence to anaemia management protocol. Use of protocol decreased within patient Hgb variability. This suggests that sustained protocol use could decrease intra-patient haemoglobin cycling. The mean and standard deviation of hemoglobin values is shown for each group in parenthesis.

Table 4. Adherence to protocol and success in anaemia management after patient censorship on hospitalization

<table>
<thead>
<tr>
<th>Adherence to protocol</th>
<th>Odds of below target</th>
<th>Odds of above target</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>EPO and iron</td>
<td>0.87</td>
<td>0.63–1.20</td>
</tr>
<tr>
<td>EPO only</td>
<td>0.73</td>
<td>0.48–1.11</td>
</tr>
<tr>
<td>Iron only</td>
<td>1.13</td>
<td>0.83–1.55</td>
</tr>
<tr>
<td>None</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.99</td>
<td>0.99–1.00</td>
</tr>
<tr>
<td>Kt/V</td>
<td>1.07</td>
<td>0.89–1.30</td>
</tr>
<tr>
<td>Initial hgb (g/dL)</td>
<td>0.40</td>
<td>0.36–0.45</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>1.009</td>
<td>1.00–1.014</td>
</tr>
<tr>
<td>PTH (100 pg/mL)</td>
<td>1.02</td>
<td>1.00–1.05</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>1.11</td>
<td>0.90–1.38</td>
</tr>
<tr>
<td>Reuse (changes per month)</td>
<td>1.00</td>
<td>0.97–1.03</td>
</tr>
<tr>
<td>Diabetic</td>
<td>1.11</td>
<td>0.90–1.37</td>
</tr>
<tr>
<td>Facility (15 sites)</td>
<td>0.41–2.53</td>
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</tr>
</tbody>
</table>

6119 patient months reduced to 4921 patient months once hospitalizations were censored.
or calculation errors), which likely resulted in decreased clinical effectiveness, increased cost and possibly excess morbidity in the form of hospitalizations.

In this study, protocol adherence to either iron or EPO dosing increased the likelihood of achieving the target haemoglobin level. The majority of this improvement stems from protocols bringing more ‘above’ patients into the target range, with relatively little effect on the number of patients who remained below target. These findings remained highly significant after adjustment for the patient and laboratory values, and are increasingly relevant given that recent prospective studies have emphasized the dangers of over treating anaemia in CKD patients [5]. Furthermore, adherence with the anaemia protocols was associated with a substantial reduction in the use of both iron and EPO, which would lead to direct cost savings in the management of the dialysis patients. While protocol adherence improved the prevalence of patients achieving target haemoglobin values, it did not reduce the risk of falling below target. It is not entirely clear why this occurred. Most likely, physicians and nurses focused hard on assuring that patients with low haemoglobin values were treated aggressively. This is supported by the fact that off protocol dosing tended to be substantially higher than per protocol. Thus, off protocol dosing was likely biased towards greater action when patients had low haemoglobin rather than high haemoglobin levels and resulted in more patients reaching above goal values. Still, this failed to reduce the number of patients below target as compared to the protocol, likely because it was reactive dosing rather than proactive.

Also, this analysis found that the population adherent to anaemia protocols not only had significantly more patients within the target range, but that the distribution of anaemia values could be made more narrow, at least as measured by standard deviation. A similar analysis of individual patient standard deviations throughout the study period suggested that protocol adherence resulted in less variability of haemoglobin. Variability in haemoglobin levels has been attributed to biologic responsiveness to anaemia and risks of dialysis treatment, and has been linked to adverse outcomes including mortality in separate observational assessments of dialysis populations [13,22]. Further, the present analysis suggests that the protocol was protective from achieving out of target haemoglobin levels regardless of the initial haemoglobin level. Additionally, the finding that patients treated on protocol did indeed receive less EPO and iron resulting in lower mean haemoglobin levels suggests that the protocol was driving drug use and influencing haemoglobin.

Nonetheless, this study is limited by selection bias and unmeasured confounding associated with its observational nature. It remains possible that the patients treated off protocol were sicker or less stable to start with, but we have fully adjusted for their laboratory values, demographics and comorbidities to limit this effect. Additionally, the analysis was done before the publication of the CHOIR [27] and CREATE [28] studies when the targeted haemoglobin in our population was higher (11–12.5 g/dL rather than 11–12 g/dL). Nonetheless, the analysis does suggest that protocol-based anaemia management is effective at achieving a predetermined target interval that can be shifted to any desired haemoglobin level.

Anaemia management is a complex clinical problem that will require an aggregate of improvements in multiple areas to achieve recognizable progress. Proper adherence to standardized EPO and iron protocols appears to positively influence multiple anaemia management outcomes while decreasing cost. Recent studies have suggested that alternate approaches, including holding EPO when the haemoglobin is high, can limit sustained above target haemoglobin levels [29]. Further improvements in clinical outcomes will likely come from improved dosing strategies and algorithms for erythropoietic agents and iron administration that account for population and individual EPO and iron responsiveness. Given the significant association between patient characteristics and success in anaemia management, factors such as EPO responsiveness, sex, parathyroid hormone and C-reactive protein might be incorporated into the algorithms for EPO and iron dosing. It would also appear prudent to implement widespread information technology to help improve adherence to such newer and increasingly complicated dosing strategies.

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References

Diagnostic potential of serum biomarkers for left ventricular abnormalities in chronic peritoneal dialysis patients

Angela Yee-Moon Wang1,*, Christopher Wai-Kei Lam2, Mei Wang1, Iris Hiu-Shuen Chan2, Siu-Fai Lui1, Yan Zhang1 and John E. Sanderson1,†

1Department of Medicine & Therapeutics and 2Department of Chemical Pathology, the Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, New Territories, Hong Kong

Correspondence and offprint requests to: Angela Yee-Moon Wang; E-mail: aymwang@hku.hk

*Current address: Department of Medicine, Queen Mary Hospital, University of Hong Kong, Hong Kong.
†Department of Cardiovascular Medicine, The Medical School, University of Birmingham, Birmingham, UK.

Abstract

Background. N-terminal-pro-brain natriuretic peptide, cardiac troponin T (cTnT) and high sensitivity C-reactive protein (hs-CRP) have been shown to predict mortality and cardiovascular outcomes in end-stage renal disease patients. However, it is not known which biomarkers have the strongest diagnostic potential for left ventricular (LV) abnormalities in chronic peritoneal dialysis (PD) patients, nor whether residual renal function may confound the diagnostic potential of these biomarkers.

Methods. Two hundred and thirty chronic PD patients underwent two-dimensional echocardiography to determine LV hypertrophy and ejection fraction and had simultaneous measurement of serum NT-pro-BNP, cTnT and hs-CRP.

Results. A significant gain in predictive power was observed when NT-pro-BNP or cTnT but not hs-CRP was included in the multivariable logistic regression models for severe LV hypertrophy (defined as LV mass index ≥ upper tertile, 247.8 g/m2) and systolic dysfunction (defined as ejection fraction ≤45%). Using ROC curve analysis,