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Original Article

Effects of haemoglobin normalization on quality of life and cardiovascular parameters in end-stage renal failure

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Abstract

Background. The optimal haemoglobin concentration ([Hb]) for patients with end-stage renal failure is uncertain. In particular, it is unclear whether Hb normalization may be an advantage to such patients who are otherwise well.

Methods. A prospective, randomized, double-blind cross-over study was completed in 14 haemodialysis patients (12 male) aged between 23 and 65 years over a period of 18 months, using a variety of measures to examine the effect of epoetin at target [Hb] of 10 g/dl ($[Hb]_{10}$) and 14 g/dl ($[Hb]_{14}$). Patients were randomized to maintain one or other of the target levels for 6 weeks before being crossed over to the alternative [Hb]. Baseline data (mean [Hb]: 8.5 ± 0.2 g/dl) were also included selectively. Six patients were known to be hypertensive. Comparisons were made between 24-h ambulatory blood pressure levels (ABP), echocardiographic findings and estimates of blood volume (BV), plasma volume (PV) and Hb mass. Quality of life estimates were obtained using the Sickness Impact Profile (SIP), and epoetin dosage requirements at target [Hb] were assessed.

Results. Daytime and nocturnal ABP (systolic and diastolic) were not different at the respective target [Hb], although nocturnal diastolic levels were higher compared with baseline (73 ± 4 mmHg) at both $[Hb]_{10}$ (83 ± 3, $P < 0.01$) and $[Hb]_{14}$ (81 ± 6, $P < 0.05$). Significant reductions in cardiac output (5.2 ± 0.3 *vs* 6.6 ± 0.5 l/min, $P < 0.01$) and left ventricular end-diastolic diameter (4.8 ± 0.2 *vs* 5.2 ± 0.2 cm, $P < 0.001$) were found at $[Hb]_{14}$ compared with $[Hb]_{10}$. Left ventricular mass index was correlated with both PV ($P < 0.001$) and BV ($P < 0.01$), but not with Hb mass. The PV decreased as the [Hb] rose ($P < 0.001$) but BV remained unchanged. Quality of life was significantly improved at $[Hb]_{14}$ compared with $[Hb]_{10}$ for both total score (6.5 ± 1.7 *vs* 13.4 ± 3.0, $P = 0.01$) and psychosocial dimension score (5.4 ± 1.9 *vs* 15.4 ± 4.0, $P < 0.01$). The maintenance weekly dose of epoetin required was 80% higher at $[Hb]_{14}$ compared with $[Hb]_{10}$ ($P < 0.001$).

Conclusion. These data suggest there may be a significant haemodynamic and symptomatic advantage in maintaining a physiological [Hb] in haemodialysis patients. Although untoward effects were not identified in this study at $[Hb]_{14}$, a substantially higher dose of epoetin is required to maintain this level.

Keywords: blood pressure and volume; epoetin dosage; haemodialysis; haemoglobin; quality of life

Introduction

Over a decade after its introduction, epoetin is now used widely for patients with end-stage renal failure (ESRF). The optimal haemoglobin concentration ([Hb]), however, remains elusive, and controlled studies examining the relative benefits of one [Hb] over another are few. The absence of objective evidence of improvement with a higher [Hb] creates confusion with regard to therapeutic goals, and discouraging reports from selected populations [1] may well result in less than appropriate strategies for other patients. The current study was designed to address the potential benefits and disadvantages of partial compared with full reversal of anaemia in haemodialysis patients who were otherwise well. The study examined symptomatic well-being, 24-h ambulatory blood pressure levels, serological changes, epoetin dosage requirements, echocardiographic analysis and estimates of blood and plasma volume. It was conducted in parallel with a recently published exercise performance study in the same group of patients [2].

Subjects and methods

Patients

Thirty out of sixty-five stable, sedentary, patients without cardiovascular, respiratory or musculoskeletal disease from

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two satellite chronic haemodialysis units agreed to enrol in a double-blind, prospective, randomized, cross-over study. Recombinant epoetin was used to compare ambulatory blood pressure levels, echocardiographic changes, blood volume estimates and quality of life at two different [Hb]: 10 ($[Hb]_{10}$) and 14 ($[Hb]_{14}$) g/dl. For some measures, comparisons were also made against baseline data (pre-epoetin [Hb]: 8.5 ± 0.2 g/dl).

Fourteen patients (12 male) completed the study and were eligible for analysis. Of the other patients enrolled but subsequently not included in the analysis, one patient died, six received a cadaveric transplant, one withdrew with significant uraemic bone disease, two were withdrawn because of poor compliance and six elected not to continue. At the start of the study, six patients required medication for control of hypertension: three were taking angiotensin-converting enzyme inhibitors, and three calcium channel blockers.

The subjects, who had been on dialysis for at least 12 months (34 ± 29, mean $\pm$ SD, range 12–59 months) before commencing the study, were assigned randomly to one of the two target [Hb] groups. They were maintained at the allocated target level for 4 weeks and during testing conducted over a further 2-week period. The groups were then crossed over and Hb maintenance and testing were repeated in an identical fashion at the alternate [Hb] (Figure 1). Each patient acted as their own control (repeated measures design).

Blood pressure and bodyweight

Ambulatory blood pressure (ABP) was measured and recorded every 20 min between 6 a.m. and 10 p.m. and hourly overnight (Spacelab Monitor 90207, Redmond, Washington, USA). Bodyweight was recorded on electronic scales (Model HVCF-150, Chemtronics, Australia) both before and after dialysis during the 2-week testing period. The mean of the results (both pre- and post-dialysis) was used for analysis.

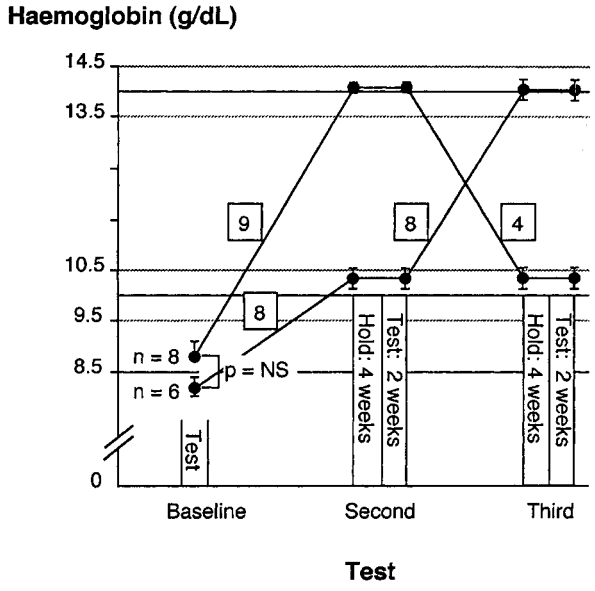

Fig. 1. Outline of study. Boxed numbers n indicate the number of months required for all patients to have reached their target [Hb]. No differences were statistically significant.

Echocardiography

Doppler echocardiography was performed using a Hewlett-Packard 1000 or 2500 scanner (Andover, Mass, USA) with 2.5 or 3.5 MHz transducers. Left ventricular septal and posterior wall thickness, end-diastolic (LVEDD) and end-systolic diameters (LVESD) were measured from the long axis parasternal plane according to the American Society of Echocardiography (ASE) guidelines. An average of three estimates was obtained in each case. Cardiac output and left ventricular mass (LVM) were calculated using standard ASE recommended formulae, and LVM was corrected for bodyweight (LVMI).

Hb mass and blood volumes

Haemoglobin mass (HbM) was measured, and estimates of blood volume (BV) and plasma volume (PV) were made in resting patients. HbM describes the molar mass of Hb circulating in the body and can be estimated accurately using the CO-Hb indicator dilution method [3]. Briefly, after breathing 100% O_2 for 4 min (via a Hans Rudolph valve with nose clip), the subject was switched to a low-volume (2 l) closed circuit rebreathing apparatus which had been flushed with O_2 and to which O_2 was added at a rate matching body uptake. After 2 min, the first (pre-) blood sample of 3 ml was obtained from the arterio-venous fistula, and the capped syringe was placed on ice. A bolus of carbon monoxide, sufficient to increase carboxyhaemoglobin levels (%HbCO) by 6–7%, was then added to the rebreathing system and after 10 min a second blood sample (post-) was obtained. [Hb] and %HbCO were measured spectrophotometrically using a diode-array spectrophotometer (OSM3, Radiometer, Copenhagen), and a microhaematocrit was obtained using centrifugation. Hb mass, BV and PV were then calculated using standard formulae [3,4].

Blood pressure recordings, echocardiographic measurements and HbM estimates were taken at the same time relative to dialysis for each patient at baseline and at both target [Hb]. For all but two patients, this was on the day following dialysis. Persons reporting and performing echo and HbM estimates were blinded to the [Hb] and all reasonable attempts were made to ensure that patients also were unaware of their own [Hb].

Sickness impact profile questionnaire (SIP)

The SIP is a standardized instrument containing 136 statements related to health-based behavioural dysfunction [5]. Statements are weighted in proportion to the degree of dysfunction attributed to them, and are grouped into 12 categories, which describe specific areas of dysfunction. These are: ambulation (A), mobility (M), body care and movement (BCM), social interaction (SI), communication (C), alertness behaviour (AB), emotional behaviour (EB), sleep and rest (SR), eating (E), work (W), home management (HM) and recreation and pastimes (RP). Scores from three of the categories (A, M and BCM) are combined to create a physical dimension (PD) score, and four categories (SI, C, AB and EB) are aggregated to give a psychosocial dimension (PSD) score. A total score is obtained from the combined weighted scores of all 12 categories. SIP scores thus represent the percentage of total possible scaled scores for 12 categories, two dimensions and an overall score. Theoretically, scores may range from 0 to 100, where the higher the score

(category, dimensional or total), the greater the degree of dysfunction.

Haemoglobin, iron stores and epoetin administration

Haemoglobin was measured weekly. Iron studies were assessed monthly and if ferritin levels were <100 mg/dl and/or iron binding saturation was $<20\%$, the patient was given an intravenous infusion of iron dextrin (1000 mg).

Epoetin was administered subcutaneously unless the required dosage exceeded 20 000 U per week, when it was given intravenously. Subcutaneous doses were administered twice weekly, intravenous doses thrice weekly. Epoetin dosage requirements were assessed during the 6-week period whilst the [Hb] was kept constant at the prescribed target level.

Other serological parameters

Plasma levels of urea, creatinine, potassium and phosphate and liver function tests (including albumin) were measured monthly. Folate and vitamin B12 levels were monitored every 3 months, and aluminium and parathyroid hormone at the beginning and end of the study.

Statistical analyses

Results are reported as the mean $\pm$ SEM unless otherwise stated. For all analyses, an α level of 0.05 was used to determine statistical significance. Comparative data were analysed using Student's paired *t*-test. Correlations were analysed using Spearman's rank test and by regression analysis; multiple samples were analysed using analysis of variance with repeated measures.

All procedures were approved by the Royal Melbourne Hospital Board of Medical Research Advisory Committee.

Results

Haemoglobin

Baseline [Hb] ranged from 6.6 to 9.9 g/dl (8.5 ± 0.2). Each target [Hb] was achieved and maintained (Figure 1) with a significant and evident rise in [Hb] ($P<0.001$). The time required to complete the study did not differ significantly between patients assigned first to the higher or to the lower target [Hb] (13.2 ± 1.1 months, $n=8$, *vs* 17.5 ± 1.7, $n=6$, respectively).

Blood pressure and body weight

Blood pressure (ABP) was analysed using mean and peak daytime and nocturnal levels. There was no difference in either systolic (SBP) or diastolic (DBP) levels between respective target [Hb] (Figure 2). In particular, there was no evidence of hypertension induced by a physiological [Hb]. There was, however, a significant increase in daytime DBP at $[Hb]_{10}$ compared with baseline (83 ± 3 mmHg *vs* 77 ± 4, $P<0.01$) and the nocturnal DBP was lower at baseline (73 ± 4) than at each target level ($[Hb]_{10}$: 81 ± 4, $P<0.01$; $[Hb]_{14}$: 81 ± 6, $P<0.05$). Overall, nocturnal ABP levels did not differ significantly from daytime readings although 11 patients were known to be hypertensive (Figure 2). Neither pre- nor post-dialysis bodyweight changed appreciably during the study (Figure 2).

Echocardiographic studies

Significant reductions in cardiac output (CO) and LVEDD were identified at $[Hb]_{14}$ compared with $[Hb]_{10}$ ($P<0.01$, Table 1). Left ventricular mass index (LVMI) was significantly lower at $[Hb]_{14}$ compared with baseline (122 ± 11 g m^2 *vs* 141 ± 13, $P<0.02$) but not compared with $[Hb]_{10}$. LVMI and LVEDD were correlated ($r=0.62$, $P<0.001$) when baseline and target [Hb] data were pooled.

Hb mass and blood volumes

Using pooled data, PV decreased progressively as the [Hb] increased ($r=-0.68$, $P<0.001$, Figure 3); BV, however, remained unchanged (baseline: 5350 ± 260 ml, $[Hb]_{10}$: 5100 ± 170, $[Hb]_{14}$: 5110 ± 160).

LVMI and LVEDD each correlated with PV ($r=0.53$ and 0.48, respectively, $P<0.01$) and with BV ($r=0.41$ and 0.48, $P<0.01$, Figure 3) but not with HbM. Similarly, there was no correlation between HbM and [Hb]. Body weight correlated significantly with BV ($P<0.02$) but not with LVMI ($P>0.3$).

Quality of life

The SIP score was significantly less at $[Hb]_{14}$ than at $[Hb]_{10}$ for both total score ($P<0.02$) and psychosocial dimension score (PSD) ($P<0.01$, Table 2). There was no significant difference between $[Hb]_{14}$ and $[Hb]_{10}$ for the physical dimension (PD) score and no difference in PD, PSD or total score between $[Hb]_{10}$ and baseline. However both the total ($P=0.001$) and the PSD score ($P<0.01$) were significantly improved at $[Hb]_{14}$ compared with baseline. The work category score at $[Hb]_{14}$ (28.0 ± 8.8) but not at $[Hb]_{10}$ (36.6 ± 7.7) was also significantly lower than at baseline (41.9 ± 7.4, $P<0.01$), suggesting that health limitations might influence the capacity for employment less at a physiological [Hb]. At $[Hb]_{14}$, six of the nine patients who were <50 years of age expressed no limitation to working because of illness, compared with two at $[Hb]_{10}$ (data not shown). All patients over the age of 55 years ($n=5$) cited poor health as a reason not to work.

Serological changes

Levels of K^+ (5.3 ± 0.2 mmol/l), urea (28.2 ± 2.1 mmol/l) and albumin (40 ± 1 mmol/l) measured initially at baseline during the first testing period were not significantly different at target [Hb] (data not shown). Parathyroid hormone levels also were unchanged at the beginning (51 ± 15 pmol/l) compared with the end (52 ± 14 pmol/l) of the study.

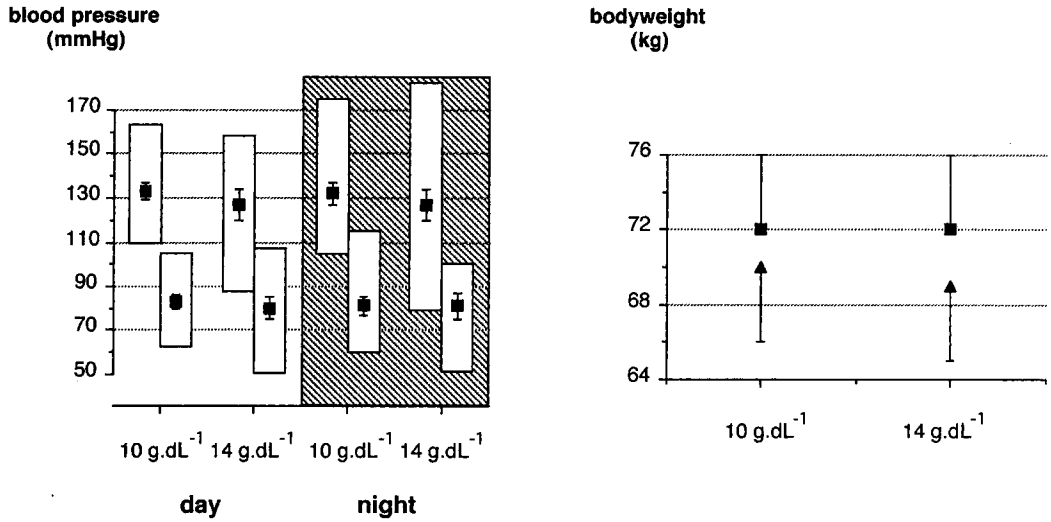

Fig. 2. Changes in 24-h ambulatory systolic and diastolic blood pressure readings (mean ± SEM and range), and pre- and post-dialysis body weight (mean ± SEM) in all subjects ($n = 14$) during the study. Readings at different target [Hb] are depicted. ■, pre-dialysis body weight; ▲, post-dialysis body weight.

Table 1. Echocardiogram results at baseline testing and at target [Hb]

	Baseline	$[Hb]_{10}$	$[Hb]_{14}$
Cardiac output (l min)	7.0 ± 0.6**	6.6 ± 0.5**	5.2 ± 0.3**
LV mass index ($g\,m^{-2}$)	141 ± 13*	128 ± 11	122 ± 11*
LVEDD (cm)	5.3 ± 0.2**	5.2 ± 0.2**	4.8 ± 0.2**
LVESD (cm)	3.4 ± 0.2	3.5 ± 0.2	3.4 ± 0.2

There were no statistical differences between baseline data and $[Hb]_{10}$ (10 g dl).
*$P < 0.02$; **$P < 0.01$.
LV: left ventricular; EDD: end-diastolic diameter; ESD: end-systolic diameter.

Table 2. SIP (sickness impact profile) results at baseline and target [Hb]

	Baseline	$[Hb]_{10}$	$[Hb]_{14}$
Work (category)	41.9 ± 7.4**	36.6 ± 7.7	28.0 ± 8.8**
Physical dimension	7.3 ± 1.6	5.9 ± 2.2	4.6 ± 2.6
Psychosocial dimension	17.8 ± 4.2**	15.4 ± 4.0**	5.4 ± 1.9**
Total score	15.1 ± 2.7***	13.4 ± 3.0*	6.5 ± 1.7*,***

The category for work capacity, physical and psychosocial dimensions and total score are demonstrated. There were no significant differences between $[Hb]_{10}$ and baseline results.
*$P < 0.02$; **$P < 0.01$; ***$P < 0.001$.

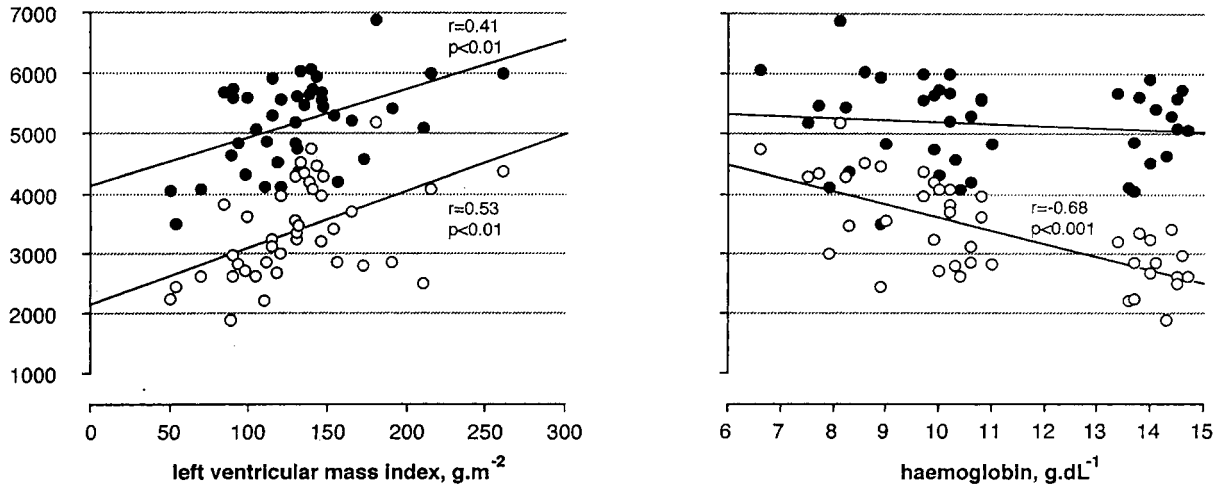

Fig. 3. Changes in total blood volume (ml) and total plasma volume (ml) in relation to left ventricular mass index and haemoglobin levels (baseline and target [Hb]). ●, total blood volume; ○, total plasma volume.

Epoetin dosage and iron requirements

The total weekly dose (all patients combined) of epoetin at $[Hb]_{14}$ was 360 000 U compared with 202 000 U at $[Hb]_{10}$ (an increase of 80%), with mean dosages of $25\,700 \pm 3200$ and $14\,400 \pm 2800$ U, respectively ($P < 0.001$) (Table 3). The range of individual requirements varied considerably: from 0 to 40 000 U per week at $[Hb]_{10}$ compared with 6000–50 000 U at $[Hb]_{14}$. Two patients at $[Hb]_{10}$ and eight patients at $[Hb]_{14}$ required intravenous epoetin because weekly requirements exceeded 20 000 U.

Five patients required an intravenous iron infusion before reaching $[Hb]_{10}$ compared with 10 (two patients twice) prior to reaching $[Hb]_{14}$.

Discussion

This study demonstrated a substantial improvement in echocardiographic parameters following normalization of [Hb]. Compared with $[Hb]_{10}$ there was a 21% reduction in CO and an 8% fall in LVEDD. The 5% reduction in LVMI was not significant although this was possibly adversely affected by the limited numbers and by the relatively brief period of time spent at respective target [Hb]. Previous studies have demonstrated that at least 3–4 months is required before a reduction in LV mass can be demonstrated following (partial) Hb correction [6–8].

Apart from anaemia, LV mass and function in chronic uraemia are known to be influenced by a variety of haemodynamic and metabolic factors [9,10]. In this respect, the correlations observed between LVMI, [Hb], LVEDD, BV and PV (Figure 3) are of interest.

Briefly, LVMI correlated closely with PV and BV but not with HbM. PV also correlated (inversely) with [Hb]; however, BV was unchanged as [Hb] increased. The apparent paradox implicit from this last finding, given the correlation between BV and LVMI, can be explained by understanding that the correlation between LVMI and BV was patient specific. In contrast to the PV where the correlation with LVMI was related mainly to the reduction in PV at each [Hb], LVMI varied according to the BV of each patient, which remained relatively constant throughout the study. Since the LV indices were standardized for body weight (LVMI), it therefore reflects the relative intravascular load for that patient which remained constant despite the changes in [Hb]. Given the constancy of other variables in the study (including blood pressure, body weight, parathyroid hormone and albumin), it highlights the critical importance of volume status (both BV and relative PV) on LVMI. It adds further weight to the suggestion that the prevailing intravascular (and hence intracardiac) volume may also be a primary determinant of LV mass and, as suggested by recent studies, eventually myocardial systolic function [11–13].

Well-being was enhanced at $[Hb]_{14}$ compared with both baseline and $[Hb]_{10}$. This is consistent with findings of the other few published studies comparing quality of life at different [Hb] [14,15]. Despite attempts to 'blind' the patients with respect to their [Hb], it is possible the increased dose required by most at their higher target could have been perceived by the patients and thus contributed to a placebo effect. How significant this might have been is difficult to determine although the lack of improvement in the physical dimension score at least suggests it was not marked. That only a small difference was found for nearly all scores between baseline and $[Hb]_{10}$ probably relates to the proximity in [Hb] for most patients. In a previous study [7], a marked improvement in well-being was identified after a modest increase in [Hb] (6.6 *vs* 9 g/dl): the baseline [Hb] was higher in this study and it may well be that there is a critical Hb level below which marked symptomatic deterioration occurs. Surprisingly little improvement in physical capacity was found at the higher target [Hb], which is consistent with the hypothesis that factors other than anaemia contribute to physical performance in ESRF [16–20]. Health limitations restricting work capacity appeared to be related to both age and [Hb]. Although the limited numbers of the current study as well as general ethical considerations preclude conclusions, such findings raise the issue of whether a differential [Hb] should be considered according to the potential for individual productivity.

The last point is particularly relevant considering the substantially higher dose of epoetin required to maintain the higher target [Hb]. Subcutaneous therapy is probably more efficient than intravenous [21,22], and the difference in dosage (and therefore cost) might have been somewhat less if subcutaneous therapy had been uniform. The pain and discomfort of three large subcutaneous injections per week, however, is signific-

Table 3. Individual and total weekly epoetin requirements ($U \times 10^3$) in order to maintain respective target [Hb] over the 6-week stabilization and testing period

Patient	$[Hb]_{10}$	$[Hb]_{14}$
1	12	20
2	4	10
3	30	40
4	10	30
5	16	24
6	20	30
7	16	24
8	4	6
9	12	42
10	20	24
11	8	20
12	0	20
13	10	20
14	40	50
Total weekly dose	202	360
Mean weekly dose	14.4 ± 2.9**	25.7 ± 3.2**

Mean weekly dose includes SEM.
**$P < 0.001$.

ant and might well have affected patient compliance. Furthermore, the observed dose differential of 80% is comparable with findings from another comparative study [14].

To conclude, the predominant findings of this study suggest that a physiological [Hb] may be advantageous for haemodialysis patients who are otherwise well. Well-being and some echocardiographic parameters were improved with Hb normalization (compared with partial correction); hypertension was not aggravated nor were other adverse events evident at the higher target [Hb]. Given the limited numbers involved in the current study, some caution is required in the interpretation of the results. However, if the findings can be corroborated by other studies, the implications of significantly improved health in the ESRF community effectively being dependent upon additional epoetin provided at a substantially higher cost need to be addressed. Should this extra cost be transferred directly to an ever-expanding national health budget? Should some patients be targeted for 'favoured' treatment because of potential productivity, or should a more attractive fee structure for epoetin be envisaged to encourage a higher maintenance [Hb] for all? The need to address such questions is already evident.

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