

SIMILAR INTRAVENOUS (I.V.) AND SUBCUTANEOUS (S.C.) WEEKLY ERYTHROPOETIN DOSES ARE REQUIRED TO MAINTAIN THE TARGET HAEMOGLOBIN IN IRON-REPLETED HAEMODIALYSIS PATIENTS WITH CORRECT ADJUVANT THERAPY: DATA FROM A PROSPECTIVE RANDOMIZED CROSS-OVER TRIAL

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REZUMAT

Introducere: Ghidurile curente recomandă ca eritropoietina (EPO) să fie administrată subcutan (s.c.) - cale asociată cu o doză mai mică necesară pentru menținerea hemoglobinei (Hb) țintă comparativ cu calea i.v., deși un număr de studii nu au găsit diferențe semnificative în necesarul de EPO între cele două căi, atât în cursul cât și după corecția anemiei și după menținerea Hb țintă. Aceasta este încă un subiect de discuții important, ținând cont de creșterea recentă a cazurilor de anemie aplastică asociate cu calea s.c.

Metode: Am hotărât abordarea diferită pentru testarea ipotezei nule. Patruzeci de pacienți hemodializați (HD) cu 1) nivele stabile ale Hb (11 g/dL cel puțin 3 luni și fără modificarea dozei săptămânale de EPO, 2) nivele serice ale ferritinei de 200-500 mg/L și TSAT (20%, și 3) PCR și albumină normale, eKT/V > 1.2 și iPTH < 3x limita superioară a normalului au fost incluși într-un studiu încrucișat, prospectiv, randomizat în care doza inițială de EPO per pacient a fost menținută neschimbată cu strictețe în cursul diferitelor perioade de tratament (recrutare, administrare s.c. - 8 săptămâni, administrare i.v. - 8 săptămâni), iar valorile individuale și medii au fost comparate pentru aceste perioade.

Rezultate: Hb medie generală pentru întreaga perioadă i.v. (prima) la pacienții din grupul A (s.c.-i.v.-s.c., N=20) a fost de 12.09±0.90 g/dL, fără diferențe semnificative față de Hb medie pentru întreaga perioadă s.c. (a doua): 11.78±0.86 g/dL. În mod asemănător, Hb medie generală pentru întreaga perioadă s.c. (prima) la pacienții din grupul B a fost de 12.17±0.87 g/dL, fără diferențe semnificative față de Hb medie pentru întreaga perioadă i.v. (a doua): 12.5±0.99 g/dL. În plus, aceste patru Hb medii au fost comparabile (p=NS pentru comparațiile intergrup). Nivelul final al Hb corespunzător pentru sfârșitul fiecărei perioade de studiu (s.c., i.v., final) nu au prezentat diferențe semnificative statistice (p=NS). În sfârșit, când s-a evaluat eficacitatea tratamentului cu EPO prin procentul de pacienți care a rămas deasupra țintei de 11 g/dL, s-a observat o tendință a creșterii numărului de pacienți sub țintă la cei din brațul i.v. → s.c. (grupul A) comparativ cu cei din brațul s.c. → i.v. (grupul B), deși per ansamblu diferențele nu au fost semnificative.

Concluzii: La pacienții HD, cu depozite de fier refăcute, cu Hb stabilă, > 11 g/dL, schimbarea căii de administrare pentru EPO de la s.c. la i.v., fără modificarea dozei săptămânale nu influențează semnificativ nivelul Hb în decurs de 8 săptămâni. Aceste dovezi prospective pun în discuție ghidurile de tratament acceptate curent, în care calea s.c. este preferată bazat pe o doză necesară mai mică.

Cuvinte cheie: anemie, eritropoietină, subcutan, intravenos, ghiduri de tratament

ABSTRACT

Background: The current guidelines recommend that erythropoietin (EPO) should be administered subcutaneously (s.c.) - route associated with a smaller dose required to maintain the same haemoglobin target compared to the i.v. route, despite a number of studies that found no significant difference in EPO dose requirement between the two routes, both during and after correction of anemia, and after maintenance of target Hb. This is still an important issue, taking into account the recently increasing number of cases of aplastic anemia mainly associated with the s.c. route.

Methods: We decided for a different approach to test the null hypothesis. Forty HD patients with 1) stable Hb levels (11 g/dL for the last 3 months, without any change in the weekly EPO dose, 2) serum ferritin levels 200-500 μg/L and TSAT (20%, and 3) normal CRP and albumin, eKT/V > 1.2 and iPTH < 3x upper assay limit were included in a prospective, randomized, cross-over trial in which the initial EPO dose per patient was maintained rigorously unchanged during the different time-periods (recruitment, s.c. -8 wks. and i.v. phase -8 wks.), and (point and mean) hemoglobin levels were compared for these different periods.

Results: Overall mean Hb level for the entire i.v. (first) period in group A (s.c.-i.v.-s.c., N=20) patients was 12.09±0.90 g/dL, non-significantly different from the overall mean Hb level for the entire s.c. (second) period - 11.78±0.86 g/dL. Similarly, the overall mean Hb level for the entire s.c. (first) period in group B patients was 12.17±0.87 g/dL, non-significantly different from the overall mean Hb level for the entire i.v. (second) period - 12.15±0.99 g/dL. Furthermore, these four mean Hb levels were comparable (p=NS, for inter-group comparisons). Final Hb levels corresponding to the end of each study period (s.c., i.v., final) were non-statistically different (p=NS). Finally, when the efficacy of the EPO treatment was assessed by the percentage of patients remaining above the target 11 g/dL line, a trend to record more cases below the target was observed in the i.v. → s.c. arm (group A) compared to the s.c. → i.v. arm (group B), but overall P=NS.

Conclusion: In iron-repleted HD patients, with stable Hb (11 g/dL), changing the EPO administration route from s.c. to i.v., without any modification in the weekly dose, does not have a significant impact on Hb levels, over a period of eight weeks. This prospective evidence challenges the current guidelines suggesting a pre-eminence of the s.c. route based on lower required doses.

Key Words: anemia, erythropoietin, subcutaneous, intravenous, guidelines.

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INTRODUCTION

The current EBPG¹ and DOQI² guidelines recommend that erythropoietin (EPO) should be administered subcutaneously (s.c.) - a route reportedly and/or reputedly associated with a smaller dose required to maintain the same haemoglobin target

compared to the intravenous (i.v.) route. This opinion was based on a number of earlier studies³⁻¹¹ some of which were small,⁶⁻⁹ included patients with a low target ferritin (100mg/L)^{6,10,11} or were conducted over a limited period of time.^{3,4,7,9} Despite the above recommendation about the optimal administration route the evidence was always mixed - for example an early randomized cross-over small study¹¹ found no significant difference in EPO dose requirement between the two routes, both during and after correction of anemia, and after maintenance of target Hb (10-12 g/dl) for an eight-week period. More recently, this view has been further supported by a prospectively randomized small study carefully controlled for confounding erythropoietic relevant factors¹² and by data from the large European Survey on Anaemia Management (ESAM) study.¹³ All these trials reported non-statistically significant different i.v. vs s.c. doses of EPO required to maintain similar Hb targets. This is now an even more important issue, taking into account the recently increasing number of cases of aplastic anemia associated with the s.c. route.¹⁴

We decided for a different, complementary, approach to test the null hypothesis. Stable, iron-replete haemodialysis (HD) patients were included in a prospective randomized cross-over trial in which the initial EPO dose per patient was maintained rigorously unchanged during the different time-periods (recruitment, s.c. and i.v. phase), and (point and mean) hemoglobin levels were compared for these different periods.

METHODS

Study population - all haemodialysis patients from the Dialysis and Transplantation Center at the Dr. C. I. Parhon University Hospital, Iasi treated with erythropoietin (EPO) were reviewed. All patients with 1- stable Hb levels >11 g/dL for the last 3 months, without any change in the weekly EPO dose, 2- serum ferritin levels 200-500 mg/L and TSAT $>20\%$, and 3) normal CRP and albumin, $eKT/V > 1.2$ and $iPTH < 3 \times$ upper assay limit, were invited to participate. 50 / 110 patients were eligible and 40 accepted to be included and signed an informed consent approved by the ethics committee.

Study design: prospective, randomized cross-over trial - the study protocol is presented in Figure 1. The selected patients - all on s.c. EPO before this study - were randomized into two groups: in group A 20 patients were switched from s.c. EPO to i.v. EPO during 8 weeks, and then were switched back to s.c.

EPO for another 8 weeks, maintaining the same pre-study weekly EPO dose during both the s.c and i.v. periods. The remaining 20 (Group B) were continued on s.c. EPO, and after 8 weeks switched to EPO i.v., similarly maintaining the same weekly pre-study dose. Both s.c. and i.v. EPO (EPREXTM) were administered by the same nurse, three times per week, at the end of the HD session. Iron status was assessed by serum ferritin and TSAT at the end of each study period. All medication was kept constant, and possible drug interference with erythropoiesis - ACE-inhibitors, cotrimoxazole, theophylline) was included in the final analysis. All patients received 25 mg of i.v. iron / week (VENOFERTM). No patients received aluminium phosphate binders in their life so a desferrioxamine test was not performed.

Drop-out criteria were defined as death, change of the RRT method, major surgery requiring at least 1 week of hospitalization and external bleeding (gastro-intestinal or genital). Three patients from group B were excluded from the final analysis due to death (N=1), severe genital bleeding (N=1) and major surgery (N=1).

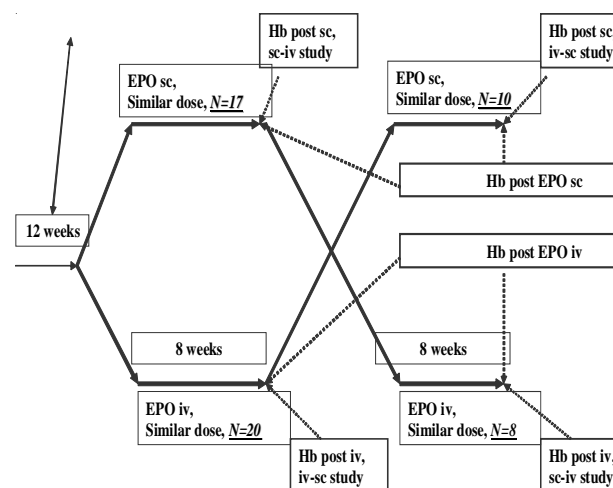


Figure 1. Study protocol (N = 40)

Statistical analysis - all patient data was included in a database and processed with a SPSS 10.0 package. Data is presented as mean and standard deviation. A paired t-test, Wilcoxon signed rank test, Mann-Whitney U test, chi-square and analysis of variance were used where appropriate. Significance was accepted for $P=0.05$.

RESULTS

Demographic and baseline parameters of the two groups are presented in Table 1. There was no significant difference between the two groups at baseline pre-randomization. All patients were dialysed

3x5 hrs/week, using an F60 filter, blood and dialysate flows of 350 mls/min and 500 mls/min. respectively. There was no infectious episodes during the study period. All patients received 25 mg of i.v. iron/week, 10 mg/day folic acid, 300 mg i.v. ascorbic acid twice a week, no co-trimoxazole or teophylline and no change in the ACE inhibitors regimens. The PTH, CRP and albumin levels remained unchanged during the study period. The serum ferritin levels and TSAT were maintained during the entire study in the same, pre-randomization range (200-500 µg/L and - 20%, respectively).

Table 1. Demographic and baseline parameters of the study groups

	Group A (N=20)	Group B (N=17)	P
Age (years)	48.2±12.4	46.7±14.7	NS
Dialysis duration (months)	65.2±31.2	56.9±37.9	NS
ESRD aetiology;			NS
diabetic nephropathy,	2	2	
chronic glomerulonephritis,	10	9	
chronic interstitial nephritis,	2	2	
other	2	1	
ADPKD	0	0	
unknown	4	3	
Gender (male / female)	11/9	10/7	NS
Hb pre-randomization (g/dL)	12.37±0.80	12.40±0.74	NS
EPO (UI/week)	6240±2439	5741±2226	NS
EPO (UI/kgc/week)	100.7±52.5	93.3±45.6	NS
Ferritin(µg/L)	443±227	347±155	NS
ACE-I (nr. patients)	2	1	NS

Patients' individual Hb values pre-randomization, following the initial 8 weeks time period, and after switching for 8 weeks to the other EPO route of administration are shown in Figures 2a (for group A) and 2b (for group B) respectively. Overall mean Hb level for the entire i.v. time period (first period) in group A patients was 12.09±/-0.90 g/dL, non-significantly different from the overall mean Hb level for the entire s.c. (second) time period - 11.78±/-0.86 g/dL (P=NS).

Similarly, the overall mean Hb level for the entire s.c. time period (first period) in group B patients was 12.17±/-0.87 g/dL, non-significantly different from the overall mean Hb level for the entire i.v. (second) time period - 12.15±/-0.99 g/dL (P=NS). Furthermore, these four mean Hb levels were comparable (P=NS, for inter-group comparisons). The final Hb levels corresponding to the end of each study period (s.c., i.v., final) are shown in Table 2. At the end of the i.v. period the difference in Hb from baseline was, in group A subjects -0.58±/-1.26 g/dL, i.e. = -4.4%, p=NS and in group B subjects -0.36±/-1.20 g/dL, i.e. = -2.6%, p=NS.

Mean group Hb level at every intermediate time point where also compared - see Figure 3.

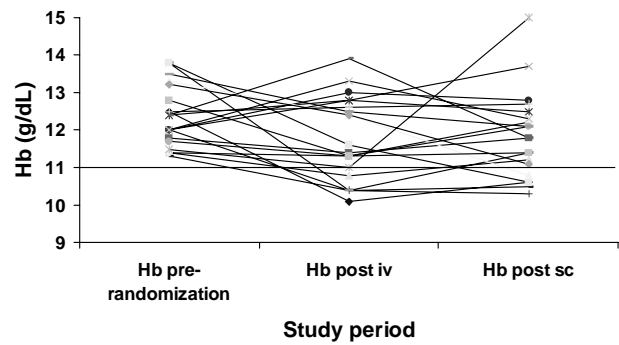


Figure 2a. Group A

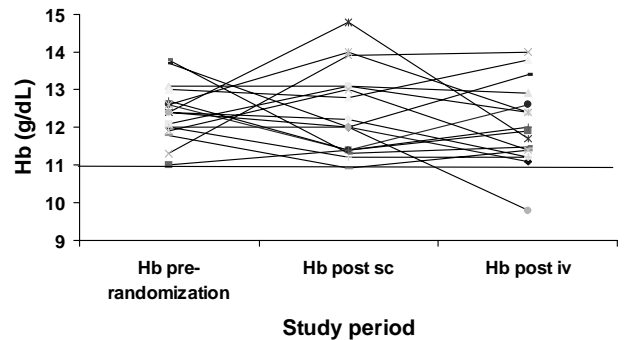


Figure 2b. Group B

Figure 2. Patients' individual Hb values pre-randomization, following the initial 8 weeks time period, and after switching for 8 weeks to the other EPO route of administration

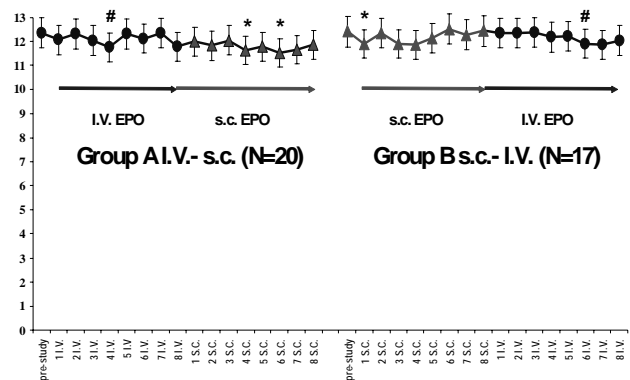


Figure 3. Evolution of mean Hb level, at different time points

In group A patients, Hb decreased significantly when compared to pre-randomization levels at the following time-points: after 4 weeks of i.v. EPO and after 4 and 6 weeks of s.c. EPO (12 and 14 weeks from start). In group B patients Hb declined significantly (when compared to pre-randomization levels) after the first week of s.c. EPO and only at the 6th week (14 weeks from start) of the second EPO period. The efficacy of the EPO treatment was also similar when it was assessed by the percentage of patients remaining above the target 11 g/dL line in the two arms (the i.v. → s.c. arm (group A) compared to the s.c. → i.v. arm (group B)).(Table 2, Figure 2a and 2b)

Table 2. Final Hb levels recorded at the end of each study period, compared to the initial / pre-randomization values

	Moment 1	Moment 2	Moment 3	P 1 vs 2 1 vs 3
	Hb pre-randomization	Hb post i.v.	Hb post s.c.	
Group A i.v. - s.c. % patients with Hb > 11 g/dL Hb level (g/dL)	100% 12.37±0.80	75% 11.79±1.11	75% 11.86±1.19	0.054, NS
Group B s.c. - i.v. % patients with Hb > 11 g/dL Hb level (g/dL)	100% 12.40±0.74	94.1% 12.04±1.09	94.1% 12.44±1.23	NS, NS

DISCUSSION

We performed a prospective, randomized study to test the alleged recommended superiority (in terms of efficiency and cost effectiveness) of the s.c. route of administration for EPO treatment. The important impact of the recognized confounders for different individual responses to EPO (i.e. iron status, inflammation, dialysis efficacy, adjuvant treatment with folic acid and ascorbic acid) was minimized by careful study design. Most importantly we chose an entirely new approach from all existing previous trials: the stable EPO dose/wk. required to maintain an individual patient Hb above the recommended EBCG and DOQI threshold^{1,2} was kept unchanged during the entire study period, irrespective of the switch to a particular route - i.v. or s.c. Finally, a cross-over design was implemented in order to minimize a possible bias determined by the sequence of administration. Under these conditions, overall equivalence between the s.c. and i.v. route was recorded, for a 16 weeks period of time.

The subject of the most economical route for EPO treatment has been debated since 1989 in 27 prospective studies including 614 patients in parallel design and 302 crossover design trials.¹⁹ The majority of these studies, including a recent meta-analysis,¹⁹ favor the s.c. type of administration, allowing a dose reduction between 15 to 70% (!) - which is the position adopted by the current guidelines.^{1,2} It has to be said that many of these initial studies are criticizable on grounds of small size,⁶⁻⁹ non-reported or non adequate iron status (by current guidelines and modern practice),^{6,10,11} limited period of observation^{3,4,7,9} or lower target Hb levels than currently accepted. The current practice has evolved (improved) significantly in the last years, most specifically in terms of better controlling the iron reserves (previously unrecognized relative iron deficiency cases). Therefore, any meta-analysis should carefully include only studies controlling the entire hematopoietic environment. Nevertheless, Besarab¹⁹ calculated that using s.c. EPO an average reduction in dose of 48 IU/kg/wk may be obtained vs the IV administration, representing an average annual cost savings of US \$1,761 +/- \$1,080 (SD) per patient.

However, this controversy is even more relevant presently in the view of the increasing concerns with increasing aplastic anemia cases most often related to the subcutaneous administration of EPREXTM. Indeed, according to current information, the risk of PRCA with Eprex® s.c. is 2.00 per 10,000 patients, compared with 0.06 per 10,000 patients when the drug is given i.v..²⁰

According to one of the largest (over 10000 patients) European surveys of clinical practice in anemia management - the ESAM study,¹³ there was only a small non-significant difference (9 IU/kg/wk) between IV and SC maintenance doses in haemodialysis patients. A critique of this findings is the fact that the hematocrit and hemoglobin levels achieved varied widely, only 53.6% of patients evaluated reached hemoglobin levels of at least 11 g/dL. Similar non-significant differences were reported in other studies.^{11,15-18} De Scoenmakere et al.¹² conducted a well-designed 12 months prospective study where the influence of iron reserves, and other hematopoietic factors was eliminated. They also found no difference between a subgroup of patients maintained on s.c. and an i.v. conversion subgroup. The impact of this conclusion was clearly diluted by the small size (only 18 subjects) and by a (non-significant) trend towards a larger EPO dose in the conversion (i.v.) subgroup, trend seen universally in the null studies. In this context our approach to keep unchanged the stable EPO dose and assessment of an eventual change in Hb brings a new and strong support to the null hypothesis. Clearly, the statistical power of numerous previous trials is reduced by the fact that a prerequisite to evaluate eventual differences between the IV and SC groups is to obtain similar maintenance hematocrit / hemoglobin levels between study arms, and usually the haematocrit target is a range (33-36%).

We believe that provided a stable and correct iron status according to the present experience and guidelines and careful attention to haematopoiesis by providing adjuvant treatment with folic acid, B6 and B12 vitamins,²¹ ascorbic acid²³ the maintenance EPO dose can be administered i.v. with similar efficacy to the s.c. route, at least for a medium (eight weeks) period of time. Iron status is particularly important since an

increase in serum ferritin levels from 52 to 534, 99 to 403 and from 111 to 609 ng/ml was associated with a decrease in the EPO dose of 70%, 61% and 75% respectively, in other studies.²⁴⁻²⁶

Our study has its limitations. A possible carry-over effect, particularly considering the 8-16 weeks observation period is possible. By inclusion criteria we have selected a stable haemodialysis population. Longer-term studies should be performed to confirm these findings, also including a control group of patients receiving less iron and no other adjuvant therapy. Nevertheless, at least in such a segment of the vast expanding dialysis pool, it is extremely probable, that even for longer periods of time, conversion from s.c to i.v. is possible without major adaptation of the EPO dose / requirements of a significantly economic increase in EPO dosage, possibly overweighing the risks of the s.c. EPO administration. To doubt has always have been one of the researcher's privileges and duties. Therefore we challenge some of the actual opinion asserting the superiority of the s.c. route.

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