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ORIGINAL ARTICLE

Cost minimisation analysis for darbepoetin alpha vs epoetin alpha in chronic kidney disease patients on haemodialysis

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KEYWORDS
Epoetin alpha;
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Abstract
Introduction: Multiple studies have shown that epoetin alpha (r-HuEpo) and darbepoetin alpha (NESP) are similarly effective and safe for maintaining haemoglobin levels in patients with chronic kidney disease (CKD). Nevertheless, there is some debate over their cost-effectiveness. The purpose of this study is to carry out a cost-minimisation analysis including a comparison of the costs to the hospital arising from treatment with r-HuEpo vs NESP.
Methods: Prospective observational study. We included CKD patients on haemodialysis with no iron, vitamin B12 or folate deficiencies, treated with stable doses of IV r-HuEpo. Follow-up was performed over three periods: the first during six months, maintaining prior treatment with r-HuEpo; the second for eight months, after changing to NESP, and the third, during the final eight months, following resuming r-HuEpo treatment. For converting both treatments, the conversion factor established on technical sheet 1:200 was used.
Results: Fifty five patients completed the study and were valid for analysis. Their mean age was 68.3 years, and 18 were women (35.3%). The mean weekly doses at the end of each period were 8,058.8 (SD 3,911.1) IU for the EPO 1 period, 39.4 (SD 21.6) mg for NESP and 7,882.4 (SD 4,594.1) IU for EPO 2. The weekly costs for each treatment showed significant differences between NESP and r-HuEpo: the cost of NESP was higher.
Conclusion: In our study, we found that r-HuEpo and NESP were similarly effective in patients with CKD on haemodialysis, but that there was a significant cost increase associated with NESP treatment.

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PALABRAS CLAVE
Epoetina alfa;
Darbepoetina alfa;
Análisis de minimización de costes;
Insuficiencia renal crónica

Análisis de minimización de costes de darbepoetina alfa frente a epoetina alfa en pacientes con insuficiencia renal crónica sometidos a hemodiálisis

Resumen
Introducción: Diversos estudios han demostrado similar efectividad y seguridad de epoetina alfa (r-HuEpo) y darbepoetina alfa (NESP) en el mantenimiento de los niveles de hemoglobina, en pacientes con insuficiencia renal crónica (IRC). Sin embargo, existe controversia en cuanto a su eficiencia. El objetivo de este estudio es la realización de un análisis de minimización de costes (AMC), y como parte del mismo se comparan los costes que supone para el hospital el tratamiento con r-HuEpo frente a NESP.
Métodos: Estudio observacional prospectivo. Se incluyeron pacientes con IRC sometidos a hemodiálisis, sin déficit de hierro, vitamina B12 o folato, tratados con r-HuEpo IV a dosis estables. El seguimiento se realizó en 3 periodos: el primero durante 6 meses, manteniendo la terapia previa con r-HuEPO, el segundo, de 8 meses, tras cambiar a NESP y el tercero, los últimos 8 meses tras nuevo cambio a r-HuEPO. Para la conversión de ambos tratamientos se utilizó el factor de conversión establecido en ficha técnica 1:200.
Resultados: Cincuenta y un pacientes completaron el estudio y fueron válidos para el análisis, con una media de edad de 68,3 años, de los cuales 18 fueron mujeres (35,3%). Las dosis medias semanales al final de cada periodo fueron de 8.058,8 (SD 3.911,1) UI para el periodo EPO 1, 39,4 (SD 21,6) mg para el NESP y 7.882,4 (SD 4.594,1) UI para el EPO 2. Los costes semanales de cada tratamiento muestran diferencias significativas entre NESP y r-HuEpo, siendo el coste de NESP superior.
Conclusión: En nuestro estudio encontramos una eficacia similar de r-HuEpo y NESP en pacientes con IRC sometidos a hemodiálisis, y un incremento significativo de los costes asociado al tratamiento con NESP.

Introduction

Erythropoietin is a glycoprotein that stimulates the proliferation of erythroid progenitors in the bone marrow. It is mostly produced in the interstitial peritubular renal cells as a response to hypoxia, which is why secretion of these cells is seen in patients with chronic kidney disease (CKD). The majority of these patients develop anaemia when their creatinine clearance falls below 30 ml/min. Furthermore, other factors also contribute to the decrease in mean lifespan of the erythrocytes, such as iron deficit, gastrointestinal haemorrhages, acute or chronic inflammation, associated infections, nutritional deficiencies, and aluminium toxicity.[1,2]

The commercialisation in Spain in 1990 of the first recombinant human erythropoietin (r-HuEpo/epoetin alpha), allowed the successful treatment of anaemia in CKD patients, improving the quality of life and survival of these patients, with an added decrease in hospital admissions. Darbepoetin alpha (NESP), commercialised in 2001, differs from the original r-HuEpo in its amino acid sequence. The mutation of 5 of these allows it to retain a greater quantity of salicylic acid, since it possesses 5 centres for N-glycosylation instead of 3, which means a greater half-life.[3,4] However, the affinity of NESP for specific receptors in the erythroid precursors is lower.[5]

The treatment with both stimulating factors is made up of a correction phase and a maintenance phase. In the correction phase, the haemoglobin (Hb) must be monitored every 2 or 4 weeks in the case of r-HuEpo, and every 1 to 2 weeks in the case of NESP, adjusting the dosage a minimum of every 4 weeks in both cases. In the maintenance phase, once the objective Hb level has been reached and the stimulation factors are stable, Hb must be monitored periodically.[4,6,7] The European Best Practice Guidelines recommend that Hb levels be maintained above 11g/dl in patients with CKD, since evidence exists that lower mortality and hospital admissions occur when the objective Hb levels are kept above clinical criteria in accordance with the individual situation of each patient.[8] In order to ensure the efficacy of the stimulation factors, adequate iron deposits are required, as measured by ferritin in the case of tissue iron, and the transferrin saturation index (TSAT) in the case of functional iron. Therefore, practically all patients require iron supplements, except for those who present with ferritin levels above 800µg/l or TSAT levels above 50%.[6,9]

Various studies have demonstrated similar effectiveness and safety with NESP in maintaining Hb levels in stable patients that had previously been treated with r-HuEpo.[10,11] In conversion studies, the NESP dosage was calculated by dividing the total weekly dosage of r-HuEpo (UI/week) by 200, the conversion factor (CF) based on the equivalence of peptide mass (200 UI of r-HuEpo alpha and 1 µg of NESP[12]). Patients treated with r-HuEpo 2 or 3 times per week passed to NESP once a week, while those patients treated with r-HuEpo once a week passed to NESP every 2 weeks.

On the other hand, a controversy exists as far as the efficiency of the two drugs. Published studies show a variety of results regarding the NESP dosage required to maintain stable Hb levels. The recommended CF for the dosage change from r-HuEpo to NESP, 200:1, is visibly different along the months of evolution in the different studies, such that results in the scientific bibliography can be found ranging from 150:1 to more than 250:1.[13-16] The requirements for NESP dosage vary from one study to another, such that they can reach higher levels, in the first case, or lower levels, in the second case, at the end of the study period.

The objective of this study was to perform a cost minimisation analysis, part of which implies comparison of the costs for hospital treatment with r-HuEpo vs NESP.

Methods

This multicentre observational study, including CKD patients undergoing haemodialysis from 2 dialysis centres working with La Fe University Hospital, took place during the period of July 2003 to December 2005.

The study was performed in 3 periods: EPO 1, NESP, and EPO 2. The first period, EPO 1, lasted 6 months (month -6 to 0). The data for the patients from this phase were retrospective. The patients started to receive NESP as an erythropoietic factor starting at month 0, and those that complied with the inclusion criteria were selected for the follow-up. The hospital policy marked the change from r-HuEpo to NESP, as it was decided to include NESP in the pharmacotherapeutic guide, substituting r-HuEpo. All of the patients came to receive NESP as a stimulation factor for erythropoiesis.

For the calculation of NESP doses, we used the CF of 200:1 (total weekly r-HuEpo dosage in UI/week divided by 200), according to the technical guidelines for NESP, the frequency of administration of the dosage was once per week for patients that received r-HuEpo 2 to 3 times a week, and every two weeks for patients who received it once a week.

In the NESP period, which lasted 8 months (months 0 to 8), the NESP dosage was adjusted in the following manner: for increases in Hb below 1 g/dl in 4 weeks, the dosage was increased by approximately 25%; for increases in Hb over 2.5 g/dl in 4 weeks, the dosage was reduced between 25% and 50%, depending on the velocity of Hb increase; in the cases where Hb surpassed 14 g/dl, the treatment was suspended until the concentrations fell below 13 g/dl, unsaturating the patient with a dosage 25% lower than the previous dosage. For the switch from the NESP treatment to r-HuEpo after month 8, we used the dosage corresponding to the total weekly NESP dosage (mg/week), multiplied it by 200, and the administration frequency was the inverse of that employed in the r-HuEpo to NESP change in the first month.

Finally, in the third phase, r-HuEpo 2 (months 8 to 18), which lasted 8 months, the r-HuEpo dosage was modified in order to achieve the objective levels of Hb.

The patients were selected based on criteria in order to prevent any influence from other external factors outside of the erythropoietic therapy.

Inclusion criteria were as follows: 1) patients older than 18 years on haemodialysis without iron deficiency (ferritin > 100 mcg/l, TSAT 20%), vitamin B12 or folate, treated with intravenous HuEpo in stable doses (weekly dosage changes < 25% in the last 8 weeks leading up to the inclusion) with stable Hb levels in the objective interval (Hb=10-13.5 g/dl); 2) patients included in the haemodialysis program for at least 6 months before the date of inclusion; 3) patients having no programmed conclusion to their haemodialysis program for the duration of the study.

Exclusion criteria included the following: 1) patients with haematological alterations; 2) patients with signs of inflammation or infection; 3) patients with uncontrolled blood pressure (BP), measured by: diastolic pressure (DAP) > 110 mmHg, systolic pressure (SAP) > 150 mmHg); 4) patients with malign pathology, except for carcinoma of the basal or squamous cells of the skin or cervical intraepithelial neoplasm; 5) patients with uncontrolled hyperthyroidism (PTH > 1500 pg/ml); 6) patients with signs of active bleeding; 7) patients who received a transfusion within 3 months prior to the inclusion.

The start date for patient recruitment is later than the communication from the Spanish Medication Agency, for which all patients received intravenous r-HuEpo along a catheter maintained for NESP delivery. Furthermore, intravenous iron was given to those patients in which it was deemed necessary, in order to maintain TSAT levels above 20% and ferritin levels > 100 µg/l.

- *Efficacy and safety:* The baseline data compiled for each patient were those corresponding to the following variables: age, sex, weight, height, body mass index (BMI), aetiology of the CKD, DAP, SAP, Hb, haematocrit (Hto), mean corpuscular volume (MCV), TSAT, serum ferritin, PTH, PRC, and blood aluminium levels.

During the study, we performed checkups every 2 months. In each case, we measured the Hb levels, as well as the dosage of stimulating factor and frequency of administration. Furthermore, information corresponding to the variables was compiled: Hb, Hto, type of iron and its dosage, TSAT, serum ferritin, blood aluminium levels, and total Kt/v.

For evaluation of the efficacy of the treatments, Hb levels were measured for each drug at the commencement and termination of each period of the study.

The descriptive statistics used for each variable were: mean and median values as parameters for position, standard deviation, range, and 25%, 75% percentiles as parameters for variation. For the comparisons of means for Hb values and treatment costs in each period of the study, we applied non-parametric tests base on the Wilcoxon test. We considered values less than $P<.05$ to be significant.

- *Costs associated with each treatment:* The study was performed from the perspective of the hospital management. For the calculation of costs associated with treatment using each drug, we took into account the price of acquisition of the medication, PVF, that corresponded to the last central purchasing competition. We did not take into account other costs, since the drug was administered through the IV route in all cases using a haemofiltration system, applying the medication through preloaded syringes.

For the calculation of weekly costs, we first obtained the weighted mean by one UI of HuEpo and 1 mg of NESP starting at the true cost to the hospital. That is, we assumed that the percent distribution of the number of consumed units

for each drug was representative of the total consumption at the hospital.

In this manner, we obtained the mean price per UI of HuEpo at 0.005584 and per mg of NESP at 1.317987.

Results

We evaluated a total of 96 patients, 90 of which complied with the inclusion criteria (Figure 1). Of these 90 patients that started with the NESP treatment, 55 patients completed the study (61.1%). The losses were due to diverse causes: 15 patients died (13.3% of the total), 6 received kidney transplants (6.7%), 3 were admitted during the study (3.3%), and 11 patients did not comply with the experimental protocol. Of the 55 patients that completed the study, 4 were excluded from the analysis for the following reasons: in 1 case, the patient would not disclose the dosage values after month 8, and 3 cases were due to possible resistance to NESP or r-HuEpo, registering increases over 10,000 UI in a 6-month period with increasing doses along the length of the study. In this way, the total number of patients valid for analysis in the study was 51, as shown by Figure 1.

The demographic characteristics of the valid patients are given in Table 1. The mean values (SD) for serum ferritin and TSAT in the first month were 493.8 (178.2) μg/l and 36.87 (14.4), respectively. Sixty-two point seven percent of patients received iron supplements, with a mean monthly dosage of 139.5 (66.9) mg.

– *Efficiency and safety:* The Hb for each month of study is shown in Figure 2. No statistically significant difference exists between the mean Hb level at the start of the EPO 1 period and the mean Hb levels at the start period (end EPO 1 and start NESP; *P*=.790), at 8 months (end NESP and start EPO 2; *P*=.318), or at 16 months (end EPO 2; *P*=.945). Neither were there statistically significant differences between the mean values at the start and end of the NESP period (*P*=.196) or between means at the beginning and end of the EPO 2

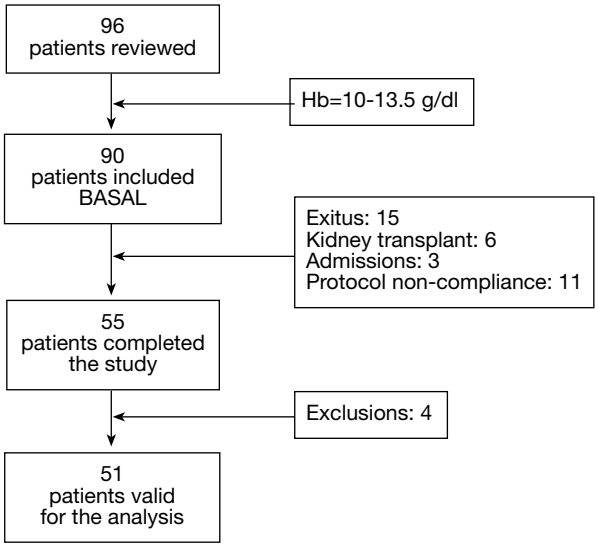

Figure 1 Patients included in the study. Hb indicates haemoglobin.

Table 1 Demographic characteristics of the patients (n=51)

Age, years	
Mean (SD)	68.3 (11.1)
Median (range)	70.5 (40.9-83.2)
Sex, n (%)	
Females	18 (35.3%)
Males	33 (64.7%)
Weight, kg	
Mean (SD)	68.0 (13.2)
Median (range)	66.0 (44.5-104)
Aetiology of the CKD, n (%)	
Glomerular	5 (9.8)
Interstitial	7 (13.7)
Polycystic	3 (5.9)
Vascular	8 (15.7)
Diabetes	7 (12.7)
Type I	4 (7.8)
Type II	3 (5.9)
Other	1 (2.0)
Unknown	20 (39.2)

CKD indicates chronic kidney disease; SD, standard deviation.

No statistically significant differences were observed in the iron dosage (*P*=.363) in the NESP period with respect to the EPO 1 period (*P*=.084), nor in ferritin levels between the NESP and EPO 1 periods (*P*=.261), nor in the TSAT (*P*=.127).

In a similar manner, no statistically significant differences were found in iron dosage (*P*=.428) between EPO 2 and EPO 1 periods, nor in the levels of ferritin and TSAT (*P*=.553; *P*=.666, respectively).

Table 2 displays the dosage of stimulation factor employed at each time period: –6 months (commencement of the EPO 1 retrospective period), month 0 (end of EPO 1 retrospective period and commencement of the NESP period), month 8 + (end of NESP period, commencement of EPO 2 period), and month 16 (end EPO 2). The change from r-HuEpo to NESP at time 0 or from NESP to r-HuEpo at month 8 is done with a CF 1:200. No significant differences were observed in the dosage between any periods (Friedman test for multiple samples: *P*=.970).

Forty-seven of the total number of patients (92.2%) passed from an administration frequency of r-HuEpo at 2-3 times a week to 1 a week with NESP. Of them, 45 maintained this frequency at the end of the NESP period and 2 dropped in frequency to 1 every two weeks. The 4 remaining patients (7.8%), passed from an r-HuEpo frequency of 1 per week to 1 every two weeks, increasing this level at the end of the NESP period in 3 cases.

In the EPO 2 period, 45 patients (88.2%) passed from a frequency of NESP administration of 1 per week, to 2-3 times a week with r-HuEpo. Of these, 34 maintained through to the end of the EPO 2 period, 7 decreased frequency of administration, and 4 increased. Three patients (5.9%) passed from NESP at once every two weeks, to once every

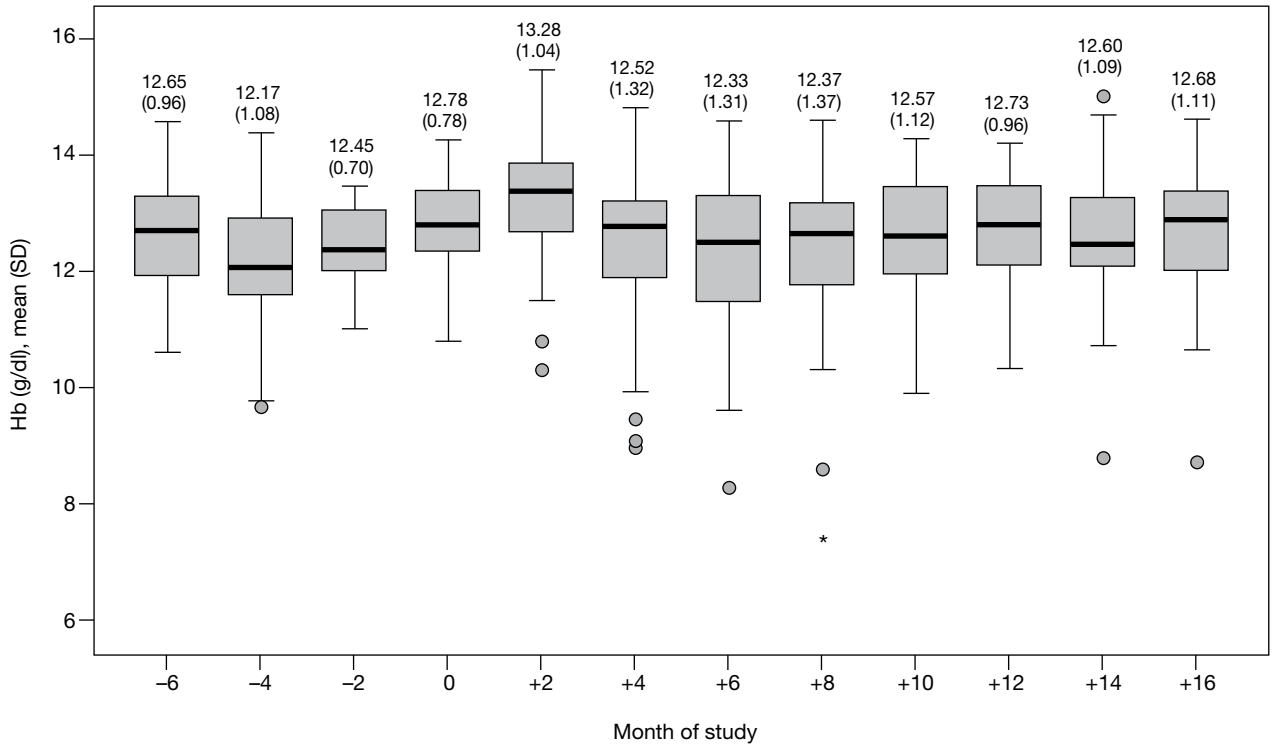

Figure 2 Mean Hb concentration during the study (SD). Hb indicates haemoglobin; SD, standard deviation.

Table 2 Weekly dosage of r-HuEpo and NESP

Period	**EPO 1 (UI)**		**NESP (μg)**		**EPO 2 (UI)**	
Month	−6	0	0	+8	+8	+16
Mean	7,784.3	8,058.8	40.3	39.4	7,882.4	7,882.4
SD	4,234.7	3,911.1	19.6	21.6	4,311.1	4,594.1
Mean	6,000	6,000	30	30	6,000	6,000
Min	0	2,000	10	0	0	0
Max	24,000	20,000	100	105	21,000	18,000
Sum dosage	39,700	411,000	2,055	2,010	402,000	402,000
Perc 25%	6,000	6,000	30	25	5,000	4,000
Perc 75%	9,000	12,000	60	45	9,000	12,000CKD

NESP indicates darbepoetin alpha; SD, standard deviation.

Table 3 Weekly costs associated with each treatment, €

Period	**EPO 1**		**NESP**		**EPO 2**	
Value of the drug, €	0.005584	0.005584	1.317987	1.317987	0.005584	0.005584
Month	−6	0	0	+8	+8	+16
Mean	43.47	45.00	53.11	51.94	44.02	44.02
SD	23.65	21.84	25.77	39.54	24.07	25.65
Mean	33.51	33.51	39.54	28.41	33.51	33.51
Min	0	11.17	13.18	0	0	0
Max	134.02	111.68	131.80	138.39	117.26	100.51
Dosage sum	2,216.85	2,295.02	2,708.46	2,649.15	2,244.77	2,244.77
Perc 25%	33.50	33.51	39.54	32.95	27.92	22.34
Perc 75%	50.26	67.01	79.08	59.31	50.26	67.01

NESP indicates darbepoetin alpha; SD, standard deviation.

week, increasing in frequency in two cases. Two patients (3.9%) maintained their frequency of administration when passing from one evaluation period to another, at 1 per week, one of whom increased at the end of the EPO 2 period. The final patient (2%) initiated the EPO 2 period with the dosage suspended, and then reintegrated into the drug program during the EPO 2 period.

– *Costs associated with each treatment:* The weekly costs for each stimulation factor are shown in the following table (Table 3). For the cost per drug unit, we used the 1:200 transformation and the mean price for each medication.

Significant differences exist in weekly costs between NESP and r-HuEpo, both in period 1 and period 2 (Friedman Test for multiple comparisons, $P>.001$).

The sensitivity analysis obtained by varying the CF from 1:150 to 1:250, the approximate minimum and maximum values found in the medical literature, are shown in Tables 4 and 5. The cut-off CF value obtained from equalising the costs of r-HuEpo and NESP is also shown.

Discussion

The results obtained in this study show a similar efficacy between r-HuEpo and NESP. The majority of patients maintained Hb concentrations within the objective ranges during the periods of the study after the inclusion process. These results are in consonance with those published by other authors, such as the multi-centric study performed in the USA and Canada with 507 patients with CKD and haemodialysis,[10] and one from Europe and Australia with 522 patients with CKD and haemodialysis or peritoneal dialysis.[11]

The CF obtained in our study is maintained around 1:200 with slight oscillations according to the period for comparison. Therefore, a CF of 1:205 is obtained comparing the final dosages of the EPO 1 period with the NESP period, and 1:200 if comparing the final dosages of the NESP period with those from the EPO 2 period. Regarding the costs, we found that the r-HuEpo treatment is associated with lower costs than NESP (€51.94 weekly at the end of the NESP treatment as opposed to €45 weekly at the end of the EPO 1 period and €44.02 weekly at the end of the EPO 2 period), when the prices employed in the study reflect those of acquisition. In this way, the price for NESP would have to drop from €1.317987 per µg to €1.142132 per mg in order to be equal with the r-HuEpo costs when considering the EPO 1 period, and to €1.117259 for the EPO 2 period.

The sensitivity analysis showed that, according to the data from our study, a CF cut-off exists (CF 1:236), at which point the costs of both erythropoietic factors are equal. Above this CF cut-off, we would predict relative cost results to favour NESP.

However, in some studies, CF values over 200:1 have been obtained. The studies by Martinez Castelao et al[17] and Molina et al[16] propose lower dosages of darbepoietin alpha, yielding Cf values of 238:1 and 260:1, respectively. De Roger et al[15] found a reduced NESP dosage (CF=275, 9:1) when passing from r-HuEpo to NESP, such that the cost diminishes following this change. This study consisted of 2 phases. The first phase consists of evaluating the EPO stage 1, 2, or 3 times a week and NESP once a week, and in the second phase, pass the patients over to NESP once every two weeks. The reduction in costs is a product of the first phase, which makes an apparent expectation for dosage reduction since the patients that pass from weekly r-HuEpo to weekly NESP

Table 4 Sensitivity analysis for the EPO 1-NESP analysis

	Mean dosage EPO, UI	Mean dosage NESP, µg	Mean weekly cost EPO, € (base month)	Mean weekly cost NESP, € (month +8)
CF 1:205	8,058.8	39.4	45	51.94
CF 1:150	8,058.8	53.7	45	70.78
CF 1:250	8,058.8	32.2	45	42.44
CF 1:236	8,058.8	34.1	45	45.00

CF indicates conversion factor; NESP, darbepoetin alpha.

Table 5 Sensitivity analysis for the period NESP-EPO 2

	Mean dosage NESP, µg	Mean dosage EPO, UI	Mean weekly cost NESP, € (month +8)	Mean weekly cost EPO, € (month +16)
CF 1:200	39.4	7,882.4	51.94	44.02
CF 1:150	39.4	5,910.0	51.94	33.00
CF 1:250	39.4	9,850.0	51.94	55.00
CF 1:236	39.4	9,301.6	51.94	51.94

NESP indicates darbepoetin alpha.

would be overdosing. Furthermore, the study only takes into account the 4 months of follow-up during the first phase. On the other hand, Brophy et al,[18] in a study that evaluated the costs of each treatment following implementation of an exchange system to substitute r-HuEpo for NESP, observed a reduction in costs, but attribute part of that reduction to the program itself, since it standardises the dosage protocol in the r-HuEpo phase. Therefore, along this line is described the influence that the weekly r-HuEpo dosages have on the implementation of a dosage protocol, without counting on variation of the control of Hb.[9]

On the other hand, CF results from the scientific literature also fall well below 200:1, such as in the study published by Jacobs et al,[13] that with a sample of over 8000 patients with haemodialysis in different European countries, concluded that 1 µg of NESP was equivalent to 176 UI of r-HuEpo. In another study presented by the European Society for Dialysis and Transplants in 2005, an analysis of the cost-effectiveness of the different erythropoietic factors was done on 138 patients with haemodialysis. They observed a significant increase in dosage when passing from r-HuEpo alpha to NESP, which naturally translates into a significant increase in costs.[19]

One of the limitations of this study was the exclusion of costs for nursing staff under the Administration, although the authors consider that this would not have a significant impact on the total cost. Similarly, the costs obtained would only allow generalisation at these hospitals in the Valencian Community, since the prices for employees are the same as in the *Central de compras* (purchase central).

Regarding the frequency of drug administration, the majority of patients in our study that passed from r-HuEpo 2 to 3 times per week to 1 per week with NESP maintained that frequency of administration at the end of the NESP period. However, of the 4 patients that passed from r-HuEpo at 1 per week to NESP at 1 per two weeks, 3 of them increased their NESP intake during the same period. The efficacy of NESP with an administration frequency of 1 per two weeks has been shown in various studies, both by IV and SC ways.[11,20] The benefits that the patients can enjoy are a lower number of injections, and the patent that can be made when the administration is through the sc route. In our study, the administration was performed through the dialysis system, which often causes this decrease to go unnoticed.

On the other hand, in order to ensure the efficacy of treatment, it is necessary to have adequate iron deposits. Absolute or functional iron deficiency is the most common cause of a poor response to the treatment of anaemia in CKD patients. The European medical guides[8] recommend a level of ferritin between 200 and 500 and a TSAT between 30% and 40% in order to maintain adequate iron deposits and avoiding overload. In our work, the levels of ferritin and TSAT are maintained within the margin recommended for the first month and each consecutive treatment period, thanks to the administration of iron by iv route in all cases where necessary.

Regarding treatment safety, we assumed that both drugs have the same safety profile as backed by other authors in several studies.[10,11,14,21] However, this assumption may constitute a small limitation in the study that would be good to keep in mind for future study designs.

In conclusion, in our study, we found similar efficacy rates using r-HuEpo and NESP in patients with CKD undergoing haemodialysis, but significantly higher costs associated with treatment by NESP.

Conflict of interest

The authors affirm that they have no conflicts of interest.

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