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Clinical and economic benefits of dialysate quality on anaemia control and erythropoietin responsiveness among chronic hemodialysis patients

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Abstract

Introduction: In chronic hemodialysis patients (CHP), micro-inflammation is an important contributor to hyporesponsivenness to erythropoiesis stimulating agents (ESA).
Objectives: The aim of this prospective and observational study was to evaluate the influence of ultrapure dialysate (UPD) on the evolution of ESA responsiveness, anaemia control and cost in CHP.
Patients and Methods: We screened CHP with renal anaemia, receiving adequate haemodialysis at our dialysis unit and on therapy with recombinant human epoetin beta (EpoB), for a follow-up during 1 year, after changing the water treatment and dialysate from conventional dialysate (<100 CFU/mL, endotoxins <0.25 EU/mL) to UPD (<0.1 CFU/ml, endotoxins <0.03 EU/mL). EpoB responsiveness was evaluated by the erythropoietin resistance index (ERI) and anaemia control and for secondary analysis by the change in EpoB cost throughout the study period.
Results: Forty-eight CHP were included. The ERI was significantly lower after conversion to UPD, mean ERI was 13.7 ± 1.9 UI/kg/wk/g/dL on conventional dialysate, decreased to 8.29 at 6 months (P = 0.01) and 8.46 UI/kg/wk/g/dL at one year. There was a significant increase in mean hemoglobin (Hb) at 6 months of follow up (12.07 ± 1.78 g/dl, P = 0.02) after conversion to UPD, and was maintained until the end of the study (11.1 ± 1.66 g/dL). Also the proportion of patients with Hb >11 g/dL increased from 17.8% at the beginning to 80.4% at month 6 (P = 0.011), and 78.5 % after 1 year.
Conclusion: UPD should be adopted as a basic component of modern dialysis procedures for improving clinical outcomes such as anaemia management and Epo responsiveness, and also for the economic benefits related to the decrease in Epo requirement.

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Introduction

In chronic hemodialysis patients (CHP), the sensibility and response of anemia to erythropoiesis stimulating agents (ESA) may be influenced by different factors: inflammation, inadequate iron loads, vitamin deficiencies, inadequate dialysis, comorbidities and infection (1,2). In this regard, inflammation and micro-inflammation are important contributors to the hyporesponsivenness to ESA (3), and they require special attention in the management of renal anaemia. Several studies have reported that most chronic kidney disease (CKD) patients have a subclinical micro-inflammatory state with high serum levels of some pro-inflammatory proteins and cytokines (4-7). Also haemodialysis (HD) therapy per se can significantly contribute to the chronic inflammation syndrome that characterizes chronic kidney disease (CKD) (8), because of production of pro-inflammatory cytokines, caused by dialyzer-induced complement activation (9), and by direct interaction between the blood cells and the hemodialyzer membrane

Core tip
Ultrapure dialysate (UPD) should be adopted as a basic component of modern dialysis procedures for improving clinical outcomes such as anaemia management and erythropoietin responsiveness, and also for the economic benefits related to the decrease in erythropoietin requirement.

(3,10). Fortunately, the quality and technology of HD has improved in relation to the biocompatibility of the materials used (11-13). In this regard, the microbiological quality in the dialysate has been suggested as a major contributor of this inflammation (14,15), and a link between dialysate purity, inflammation, and responsiveness to ESA is suggested by different studies (16-18), with the background idea that microbiologic contaminants in the dialysate and level of endotoxin might induce inflammation and resistance to ESA in dialysis patients (3,8,9,19,20).

Objectives

The aim of this prospective and observational study was to evaluate the influence of ultrapure dialysate (UPD) on the evolution of ESA responsiveness, anaemia control and cost in CHP.

Patients and Methods

Patients

Adult patients with chronic renal anaemia, receiving adequate HD (KT/V ≥1.2, at the dialysis unit of the Military Hospital of Agadir in Morocco, were screened for inclusion in this study. They were required to be on therapy with recombinant human epoetin beta (EpoB) (Recormon®; Hoffman-La Roche Ltd, Basel, Switzerland), for at least 12 weeks, with Adequate iron levels (ferritin > 200 µg/L, transferrin saturation [TSAT] > 25%). We excluded those who had been on dialysis for fewer than 3 months, who had received blood transfusions, experienced bleeding episodes. CHP that complied with the inclusion criteria were selected for a follow-up during 1 year maintaining prior treatment with EpoB thrice weekly.

Study design

It was a prospective observational cohort study, selected patients were receiving usual dialysis care, and they not required to undergo any additional medical interventions, tests or procedures. We changed water treatment system of our dialysis unit and we added an endotoxin filter on dialysate circuit, to switch it from conventional dialysate (defined as containing bacteria: colony forming units < 100 CFU/mL and endotoxins <0.25 EU/mL) to UPD defined in the pharmacopeia as containing <100 CFU/L (or <0.1 CFU/mL) and endotoxins <0.03 EU/mL with sensitive kinetic chromogenic Limulus amoebocyte lysate assay (LAL) (8,18,21). Microbiological monitoring of dialysis fluid has been maintained every 3 months during 1 year; to verify bacteriological and endotoxin level conformity, within the range recommended by the International Organization for Standardization; ISO 11663:2009 (22) and ISO 23500:2011 (23) norms for UPD adopted by the Moroccan society of nephrology norms for dialysis facilities (24). The following laboratory parameters were gathered for patients at the beginning of the study, and were repeated monthly during the follow-up: hemoglobin (Hb), red blood cell (RBC) count, hematocrit (Hct), platelet count, serum iron, TSAT, ferritin, serum intact parathyroid hormone (iPTH), C-reactive protein (CRP), protein, albumin, glucose, blood urea nitrogen (BUN), creatinine (Cr), sodium (Na), potassium (K), calcium (Ca), phosphate (P).

Treatment procedures

Patients were on conventional HD three times a week schedule, using the 4008-S FMC machine and synthetic polysulfone, low-flux dialyzers Fx-class (Fresenius Medical Care, Bad Homburg, Germany). The weekly doses of EpoB beta were adjusted to keep Hb within the range 10-12 g/dL, and iron dose was adjusted to keep ferritin over 200 µg/L. Water treatment system consisted on double reverse osmosis, classic pre-treatment (softener, activated carbon, and microfiltration), distribution loop with permanent water circulation and direct delivery to dialysis machines). To produce UPD, we equipped dialysis machines with two endotoxin ultrafilters, ensuring a final cold sterilization of the dialysate. The study design is summarized in Figure 1.

EpoB responsiveness

To evaluate EPO responsiveness, we used the erythropoietin resistance index (ERI), defined as the weekly weight-adjusted EpoB dose (U/kg/wk) divided by Hb level (g/dL). For secondary analysis, we analysed the evolution of mean Hb and the proportion of patients with Hb >11 g/dL based on a 3 months average.

Cost analysis

A health care payer perspective was adopted, for a time horizon of one year. Costs were obtained from the prices approved by the Moroccan Agency on Medical Insurance (ANAM). They were collected every three months for each patient, based on EpoB acquisition costs, then were averaged across patients. All costs were collected in Moroccan dirhams (MAD) and converted to US dollar (US$1 = 9297 MAD).

Ethical issues

The study was conducted in accordance with the Declaration of Helsinki, International Conference on Harmonization Good Clinical Practice guidelines, and local ethics committees. All study participants provided informed consent. The research was approved by the Ethics Committee of Mohammed V University, Rabat.

Statistical analysis

Results are expressed as percentages for discrete variables, continuous data were tested for normality by the Kolm-

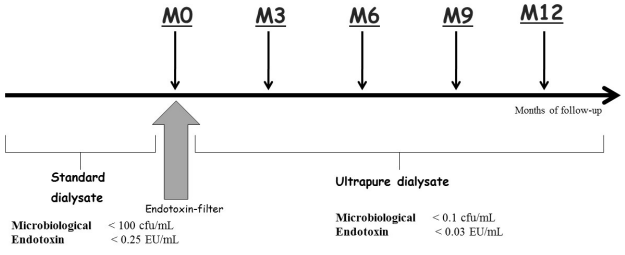

Figure 1. Design of the study.
M: month since inclusion

ogorov-Smirnov test and were expressed as mean ± standard deviation (SD) or median and interquartile range, and clinical significance was assessed by Friedman's F test. Analyses were performed with SPSS 18 (SPSS Inc., Chicago, IL, USA); results were considered statistically significant with $P < 0.05$ (two-tailed comparison).

Results

Table 1 lists demographic and baseline characteristics of dialysis patients included. In total, 48 CHP have completed the study and were valid for the analysis. 28 men (58.4%) and 20 women (41.6%), with a mean age of 52.3 ± 25.1 years, on HD since 48.20 ± 20.7 months, diabetic nephropathy was the most common cause of end stage renal disease.

Clinical efficacy

The ERI was significantly lower after conversion to UPD, mean ERI was 13.7 ± 1.9 UI/kg/wk/g/dL on conventional dialysate, decreased to 8.29 at 6 months ($P = 0.01$) and 8.46 UI/kg/wk/g/dL at one year (Figure 2). Baseline Hb level was 9.27 ± 123 g/dL, there was a significant increase at 6 months of follow up (12.07 ± 1.78 g/dl, $P = 0.02$) after conversion to UPD, and was maintained until the end of the study (11.1 ± 1.66 g/dL). Also the proportion of patients with Hb >11 g/dL increased from 17.8% at the beginning to 80.4% at month 6 ($P = 0.011$), and 78.5% after 1 year, with a significant decrease in weekly EPO dose (127.2 ± 23.1, 100.14 ± 33.2 and 94.3 ± 15.2 UI/kg/wk at baseline, 6 months and at 12 months, respectively). Evolution of Hb, EPO dose and the proportion of CHP with Hb >11 g/dL during the study are summarized in Table 2. There were no significant differences as compared to baseline for dialysis dose, iron storage and iPTH, however, we observed a decrease in CRP level and an increase in albumin concentration throughout the study period as reported in Table 3.

Table 1. Demographic and baseline characteristics

Parameters	mean ± SD or n(%)
Patients	48
Age (years)	52.3 ± 25.1
Female sex, n (%)	20 (41.6)
History on dialysis	48.20 ± 20.7
Primary nephropathy (%)	
Diabetes	30.4
Interstitial nephropathies	10.9
Glomerulonephritis	10.3
Others	29.2
Vascular	19.2
Haemoglobin (g/dL)	9.24 ± 1.23
Ferritin (ng/mL)	300.67 ± 98.2
Transferrin saturation (%)	22.5 ± 5.5
Albumin (g/dL)	35.34 ± 2.1
CRP (mg/dL)	8.89 ± 2.74
Kt/V	1.21 ± 0.2
iPTH (pg/mL)	311.77 ± 65.2
Dry weight (kg)	61.34 ± 5.6
EpoB weekly dose (IU/kg/wk)	127.2 ± 23.1
ERI (IU/kg/wk/g/dL)	13.7 ± 1.23

Abbreviations: CRP, C-reactive protein; iPTH, intact parathyroid hormon; EpoB, epoetin beta; ERI, erythropoeitin resistance index.

Cost benefits

Three-month average of EPO acquisition cost decrease significantly after 6 months of follow-up as reported in Figure 3. Based on the 12-week Epo B acquisition costs, the per-patient impact was $907.5 ± 89 at the beginning of the study, significantly lower at month 6 and 12 of follow-up ($715.7 ± 56.2 and $740.4 ± 47.1 after 6 and 12 months respectively; with 24% decrease, $P < 0.01$).

Discussion

Our study shows that the use of UPD is associated with better control of anaemia in a prospective follow-up, of a cohort of chronic HD patients, with a significant decrease in erythropoiesis resistance index and erythropoietin requirement. Our finding is in agreement with data reported in several studies (3,9,19,25) that had evaluated the effect of UPD on anaemia management; and reported signs of improvement of erythropoietin response, manifested either by decrease in EPO requirement to maintain a certain Hb or increase in Hb levels in response to a constant EPO dose (26). Molina et al (3), in a study developed to assess the influence of UPD on darbepoetin responsiveness in 94 HD during 52 weeks of follow-up, had reported a significant decrease in the ERI and EPO doses; also, followed patients reach higher Hb levels after the use of UPD. These observations were confirmed by Susantitaphong et al (18),

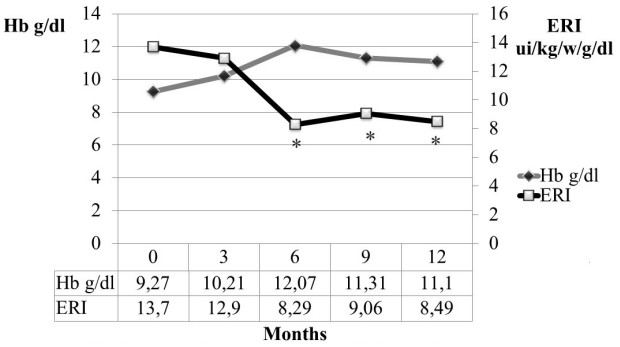

Figure 2. Evolution of ERI and Hb during the study.
*$P < 0.01$ in comparison baseline. ERI, erythropoeitin resistance index; Hb, haemoglobin.

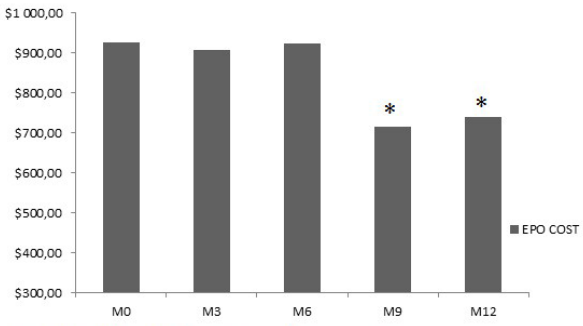

Figure 3. Evolution of EPO cost during the study.
*$P < 0.01$. EPO, erythropoeitin; M, months.

Table 2. Evolution of Hb, EpoB doses and anaemia control throughout the study

	Baseline	M3	M6	M9	M12	p
Hb (g/dL)	9.27 ± 1.23	10.21 ± 1.87	**12.07 ± 1.78**	**11.31 ± 1.9**	**11.1 ± 1.66**	0.02
Patients with Hb > 11 g/dL (%)	17.8	33.3	**80.4**	**76.6**	**78.5**	0.011
EpoB dose UI/kg/Wk	127.2 ± 23.1	131.86 ± 43.2	**100.14 ± 33.2**	**102.4 ± 44.9**	**94.3 ± 15.2**	0.03

Abbreviations: M, month; Hb, haemoglbin; EpoB, epoetin beta.
Significant differences in comparison to baseline are in bold.

Table 3. Evolution CRP, albumin, iPTH, ferrin and KT/v throughout the study

	Baseline	M3	M6	M9	M12	p
iPTH (pg/ml)	311.77 ± 65.2	390.2 ± 78.2	389.4 ± 89.2	400.2 ± 91.5	333.90 ± 77.3	0.23
KT/v	1.21 ± 0.2	1.19 ± 0.32	1.26 ± 0.4	1.27 ± 0.4	1.25 ± 0.22	0.1
Ferritin (ng/mL)	300.67 ± 98.2	400.2 ± 88.3	395.1 ± 79.2	388.23 ± 121.3	411.87 ± 112.3	0.09
CRP (mg/L)	8.89 ± 2.74	6.1 ± 0.36	**5.03 ± 1.1**	**4.41 ± 0.79**	**4.13 ± 1.2**	**0.021**
Albumin (g/L)	35.34 ± 2.1	35.67± 2.89	**37.33 ± 3.01**	**39.23 ± 3.23**	**40.13 ± 2.78**	**0.014**

Abbreviations: M, month; CRP, C-reactive protein; iPTH, intact parathyroid hormon.
Significant differences in comparison to baseline are in bold.

in a meta-analysis that examined the effect of ultrapure versus standard dialysate on markers of inflammation, oxidative stress, nutrition and anaemia parameters. Analysis of 23 study arms or cohorts (n = 2221), UPD resulted in a significant increase in Hb (0.40 g/dL; 95% CI 0.06, 0.75; $P=0.022$) and serum albumin (0.11 g/dL; 95% CI: 0.02, 0.19; $P=0.011$), a decrease in weekly erythropoietin dose (−273 units; 95% CI: −420, −126; $P<0.001$), in markers of inflammation and in C-reactive protein (−3.2 mg/L; 95% CI: −4.6, −1.8; $P<0.001$), the results remained significant in analyses restricted to controlled trials. This is in agreement with our finding of enhancement of albumin level and better inflammation status, as CRP decrease significantly during the follow-up. It is well documented that in dialysis patients, the inflammation is multifactorial and include exposure to dialysate bacterial contaminants (15), repeated exposure to bacterial products from dialysis fluid might aggravate an existing inflammatory condition. In this regard, the improvement in the EPO responsiveness following the conversion to UPD suggest the implication of pro-inflammatory cytokines such as CRP, TNF-α and IL-6 (3,9), that may decrease the intracellular sensitivity to erythropoietin (27). This hyporesponsiveness is also associated with protein-energy wasting and inflammation (18,19) and has been linked to an increased mortality risk (28). This is why UPD offers the promise of decreasing markers of inflammation and oxidative stress while improving anaemia control and nutritional parameters. Optimizing EPO doses result in a significant cost saving in our study. The economic benefits associated with the use of UPD in relation to EPO requirement decrease, should encourage its generalizability in dialysis centers, and can counterbalance the investment in water treatment to produce UPD. Moreover, in view of the wild usage of ultrapure water in dialysis facilities in recent years, the extra cost associated at UPD usage, is related to the periodic change of the endotoxin filter and additional microbiological monitoring as reported by Canaud et al (8); in a 5 years cost analysis study, the additional cost was estimated at 5 euros/dialysis session in comparison to conventional dialysate.

Conclusion

To conclude, UPD should be adopted as a basic component of modern dialysis procedures, for improving clinical outcomes such as anemia management and EPO responsiveness, and also for the economic benefits related to the decrease in EPO requirement.

Limitations of the study

Our study has some limitations; in relation the initial design adopted, we were unable to elaborate health economic study such as cost-effectiveness or a cost-minimization study. We considered only direct medical cost in relation to drug acquisition. In the next researches it would be interesting in the analysis to include other direct medical costs (iron consummation, hospitalisations and adverse events) and other relevant clinical outcomes (quality of life, number of transfusion, and infection).

Authors' contribution

OM, and SA participated in the conception and design of the study, interpretation of the data and drafting of the work; YC participated in design of the work and revising it critically for important intellectual content; NZ and DE participated in the acquisition and analysis of the data; HD participated in the interpretation of the data and revising it critically for important intellectual content; OZ participated in the conception and design of the work, interpretation of the results, and revising it for critically important intellectual content. All authors read and approved the final manuscript.

Conflicts of interest

None to be declared.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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None.

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