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Full Length Research Paper

Adherence to clinical practice guidelines for anemia among Mexican chronic dialysis patients

Catarina Munguía Miranda [1], María-de-Jesús Ventura [1], Marcela Ávila-Díaz [1], María del Carmen Prado Uribe [1], Carmen Mora Villalpando [1], Begoña Ilabaca[2], Héctor Hinojosa Heredia [3], Alfonso M. Cueto Manzano [4], Pedro Trinidad Ramos [5], Ramón Paniagua [1].

Unidad de Investigación Médica en Enfermedades Nefrológicas, Hospital de Especialidades, Centro Médico Nacional Siglo XXI [1], Hospital General de Zona A1 [2], Hospital general de Zona 47[3], Departamento de Nefrología y Unidad de Trasplante del Hospital de Especialidades, CMNO [4], Hospital de Especialidades, Centro Médico Nacional, Siglo XXI [5].

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We analyzed adherence to Clinical Practice Guidelines (CPGs) for anemia in dialysis patients, and the frequency with which the target ranges for treatment parameters were reached. A questionnaire to analyze retrospectively the adherence to CPGs for anemia was performed. Patient's files were reviewed and extracted demographic, clinical, laboratory and treatment data. In a cohort prospective study, we made clinical measures of hemoglobin (Hb), hematocrit (Htc), iron (Fe), transferrin (TF) and transferrin saturation (TSAT). Adherence was based on frequency of biochemical evaluations and the target ranges for the variables studies in the 2008 version of the KDOQI guidelines for anemia management. 573 patients were studied, 25% of the clinical files lacked recording of Hb and Htc. Less than 10% of the patients had one or more reports of ferritin or serum iron and none had reports of TF or TSAT. Only 40% of patients were within the limits of Hb suggested by CPGs. Over 60% of the patients had TSAT normal. Our data showed low degree of adherence to CPGs for anemia. The frequency with which the target ranges were reached was far of theoretical objectives.

Key words: Anemia; Adherence; Chronic Kidney Disease; Clinical Practice Guidelines; Hemodialysis;Peritoneal Dialysis.

INTRODUCTION

Anemia is one of the earlier and most frequent manifestations of chronic kidney disease (CKD) and is a consequence of the deficient production of erythropoietin (Eschbach et al., 1985; Lankhorst et al., 2010; McGonigle et al., 1884; Astor et al., 2002).CKD affects iron metabolism in various ways, it reduces its absorption from the intestineand frequent presence of chronic inflammation alters absorption and generates a redistribution of iron stores, causing a relative deficiency (Babbit et al., 2012; Slotki 2005).

In patients with CKD in treatment with dialysis, anemia is a common finding and has been associated with higher morbidity and mortality (KDOQI; National Kidney Foundation 2006; Foley et al., 1996; Kalantar-Zadeh 2009). Treatment of anemia requires the use of erythropoiesis-stimulating agents (ESAs) (Winearls et al., 1986; Eschbach et al., 1987; Eschbach 1989;) and the parenteral administration of iron (Besarab et al., 2010; Hörl 2007) and frequent monitoring of Hb levels, Festores and factors that might interfere with the pharmacological

Corresponding author. E- mail: ramon.paniagua@imss.gob.mx; jrpaniaguas@gmail.com; Tel. +52 (55)5627-6900 (21209).

effect of ESAs, which cause important impacts in the cost of medical care (Cotter et al., 2004; Paoletti et al., 2006). Due to frequency, importance and cost of anemia in patients on dialysis, clinical practice guidelines (CPGs) have been developed to standardize the detection, care and treatment of anemia (NKF-DOQI clinical practice guidelines for the treatment of anemia of chronic renal failure. National Kidney Foundation-Dialysis Outcomes Quality Initiative 1997; KDOQI Clinical Practice Guideline and Clinical Practice Recommendations for anemia in chronic kidney disease: 2007 update of hemoglobin target and European 2007; Locatelli et al., 2004). Adherence to CPGs and the high number of patients with indicator values within the limits suggested in the CPGs are now considered as indicators of the quality of care given and recently have been taken into account as factors that influence the payment to care providers in the treatment of renal patients.

There is little information about the actual implementation of CPGs on the treatment of anemia in peritoneal dialysis (PD) and hemodialysis (HD) units. One of the most controversial aspects has been the target Hb levels. Unfortunately, few studies have been published on anemia in PD. Most major observational studies and all clinical trials on this subject have been conducted in patients on HD or patients with chronic kidney disease. As such, the guidelines extrapolate these data to PD without considering the differences between the patients' profiles and the characteristics of each technique.

In México, there was no information about knowledge, acceptance and implementation of these guidelines. Nevertheless, the costs derived from whether or not CPGs are observed may be even greater than in developed countries. The aim of this study was to analyze adherence to CPGs and the frequency with which the target ranges for treatment parameters were reached.

MATERIAL AND METHODS

Design

A cross-sectional study was performed through retrospective questionnaire to analyze adherence to CPGs for anemia in patients on different dialysis modalities. The survey was followed by a cohort study to prospectively analyze the impact of adherence to guidelines on clinical outcomes. The protocol was approved by the Research Committees of 14 hospitals belonging to the Instituto Mexicano del Seguro Social (IMSS) that participated in the study, and informed consent was obtained for all patients included.

Patients

A total number of 573 patients aged >18 years old were included in this study. They were prevalent in the different dialysis modalities. Two hundred and thirty patients undergo continuous ambulatory peritoneal dialysis (CAPD); one hundred and thirty-five on automated peritoneal dialysis (APD); two hundred and eighty four on hemodialysis (HD) in IMSS hospitals

and one hundred and four on external private facilities under contract with IMSS (sHD). Patients were randomly selected from a lists of the participating hospitals by members outside the group of dialysis treatment. There was no selection by age, gender, cause of kidney disease or time on therapy. Patients were excluded if they presented acute infections or complications during the month prior to the beginning of the study, if they were seropositive for HIV, had cancer or were in treatment with immunosuppressants. Conventional treatment for HD was three 4-hour sessions a week. CAPD patients received 4 exchanges of 2L daily with dextrose solutions. APD patients received conventional schemes of treatment with dextrose solutions.

Data collection

In the cross-sectional study, trained research nurses reviewed the clinical files of the selected patients and extracted demographic, clinical, laboratory and treatment data in standardized forms. The data obtained included age, gender, diagnosis of diabetes, weight, height, body mass index (BMI) and time on dialysis. Laboratory data included Hb, Htc, Fe, TF and TSAT in serum, obtained in the six months prior to the survey. If the file showed more than one measurement, the average value was analyzed.

In the cohort prospective study, blood pressure was measured at baseline by qualified research nurses using standardized techniques and a blood sample was obtained from each patient after overnight fast. For patients on HD, the sample was taken on a non-dialysis day (mid-day) between the first and second session of the week (mid-week). From the total blood, were measured Hb, Htc and Fe (Atomic absorption spectrometry in a Perkin-Elmer 100 Analyst), as well as,TF and (Hitachi 902 Automatic Analyzer, Roche Diagnostics, GMBH Mannheim, Germany) in a central laboratory.

Adherence to clinical guidelines was based on the frequency of biochemical evaluations and the target ranges for the variables studies in the 2008 version of the KDOQI guidelines for anemia management. Patients were followed prospectively for 16 months and the following data were collected: hospitalization, days in hospital, and changes in dialysis modality, death, and cause of death.

Statistical Analysis

Continuous data are presented as means and standard deviations (SD) and discrete data as percentages. For comparisons between groups, one-way ANOVA or Student's t test was used for continuous variables and X^2 for percentages, as appropriate. For survival analysis, univariate and multivariate Cox proportional hazards analyses were performed. Patients were followed until they died, were lost to follow-up, were transplanted, or until the end of the study (16 months). Independent varia-

bles included age, gender, diabetes, weight, height, systolic and diastolic blood pressure, and laboratory values (serum glucose, blood urea nitrogen (BUN), creatinine, cholesterol, triglycerides, albumin, Hb, HTc, serum Fe, TF, TSAT,C - reactive protein). Variables that were significant in the univariate analysis were entered in the multivariate analysis using a step-forward method. Since the prevalence of diabetes varied with dialysis modality, modalities were categorized as modality with or without diabetes. All statistical analyses were performed with the Statistical Package for Social Sciences (SPSS-PC), version 18 (SPSS, Chicago, IL, USA).

RESULTS

A total of 753 patients were studied. Distribution by dialysis modality and main characteristics are shown on Table 1. They had an average age of 48±17; 55% were men and 44% were diabetic subjects. Recorded information about the follow-up of anemia indicators was irregular and limited. 25% of the clinical files lacked recording of Hb and Htc measurements within the six months prior to the survey (Table 2). Less than 10% of the patients, regardless of modality, had 1 or more reports of ferritin or serum iron over the same period, and none of the patients in CAPD had reports of ferritin, while none of the patients in any modality had reports of transferrin or transferrin saturation.

Table 3 shows levels of Hb and Htc in all modalities, as well as the numbers of patients within the target ranges and the percentage below and above these levels. It should be noted that only about 40% of patients were within the limits. Table 3 also shows a TF mean of 194±54 mg/dL; serum Fe mean of 90 µg/dL and shows as only 60% of the patients had TSAT within the limits suggested by CPGs.

In Table 4, we showed the treatment of anemia. Of the ESAs, erythropoietin-β, was the most frequently used, but in less than 25% of the patients and only 13.5% of patients in CAPD received it. Folic acid was used in about 40% of the patients, with highest proportion in PD patients. Iron was used in about 25%, but only half of patients in the HD group received this treatment. Vitamin D was used in about one-third of the patients, regardless of treatment modality. Transfusions were commonly used; most of the patients received it.

A total of 182 deaths (24%) occurred during 16 months of follow-up. Of these, 85 (47%) were due to cardiovascular disease (myocardial infarction, heart failure, arrhythmia, stroke, or sudden death), 30 (16.5%) to infection (peritonitis in 9 and other infections in 21), 22 (12%) to electrolyte disorders or other dialysis-related complications, 20 (11%) to various causes and 25 (14%) to unknown causes. Differences between survivors and non-survivors are shown in Table 5. Older age, diabetes, higher systolic blood pressure, higher serum glucose, higher corrected Ca by albumin, and lower serum albumin, P, and PTH levels were seen in non-survivors.

DISCUSSION

There is little information about implementation of clinical practice guidelines for the treatment of anemia in PD and HD units. Some data come from observational studies or foreign records that do not adequately consider the temporal evolution. Since the first guide published in 1997 (NKF-DOQI clinical practice guidelines for the treatment of anemia of chronic renal failure. National Kidney Foundation-Dialysis Outcomes Quality Initiative 1997), have been published more than 25 worldwide, although many of them are a transposition of American (KDOQI Clinical Practice Guideline and Clinical Practice Recommendations for anemia in chronic kidney disease: 2007 update of hemoglobin target and European 2007; Locatelli et al., 2004). In this study, the information about anemia indicators was irregular and limited, approximately 25% of the medical records reports Hb and Htc measurements during six months prior to the survey. Few patients in all dialysis modalities had ferritin and iron reports, and no patient had reports of transferrin or transferrin saturation. The European Survey on Anemia Management (ESAM) (Jacobs et al., 2000), observational and prospective study on the most common parameters of anemia in dialysis patients, that included 14 countries in Western Europe, revealed that the percentage of patients who reached the recommended guidelines on anemia levels in dialysis were still low. Also, ESAM 2003 a randomized survey conducted to assess anemia management in dialysis patients 4 years after the introduction of the European Best Practice Guidelines which included 8,100 patients from 11 European countries and Israel showed Hb levels ≥11.0 g/dl in 66% of patients, as was recommended by the guidelines. Only 48% of patients had adequate iron status, with transferrin saturation values missing for 27% and functional or absolute iron deficiency reported for 17% and 9%, respectively. The comparisons between the eight countries that participated in ESAM 2003 and the original ESAM revealed that many patients still have Hb levels below the current recommendations despite significant improvements in management of renal anemia over the last 5 years (Jacobs et al., 2005).

In our study, when screening tests for anemia were performed in a central laboratory, Hb levels were lower to 11% g/dL in 35% of our patients, percentage lower to be found in a study carried out by Sthunin included 41, 919 patients on dialysis, which showed that over 50% had lower levels to 11 g/dL(of Sthun et al., 2005; Bárány et al., 2003).

Table 1. Demographic and clinical characteristics.

	CAPD	**APD**	**HD**	**HDs**	**Total**	***p***
n	230	135	284	104	753	
Age (year)	55.5±13.7	41.9±19.9	46.6±18.1	47.6±15.5	48.6±17.6	<0.001
Gender (%)						Ns
Female	44	42	49	38	45	
Male	56	58	51	62	55	
Diabetes (%)	62	40	35	34	44	<0.01
Weigh (Kg)	64.9±12.5	59.2±19.9	62.4±12.5	64.2±14.6	62.8±15.8	<0.01
Height (cm)	158±10	157±12	156±12	159±9	157±11	Ns
BMI (Kg/m2)	26.13±5.14	24.44±7.31	25.03±5.03	25.32±4.95	25.30±5.55	0.028
W/H ratio	0.95±.06	0.95±.05	0.97±.54	1.01±.79	0.97±.44	Ns
Time on dialysis (mo)	30.2±36.5	31.5±32.6	52.9±55.1	50.6±45.9	41.8±46.3	<0.001
SBP (mmHg)	140.37±23.85**	131.34±22.68‡‡	143.44±26.92	138.23±25.39	139.62±25.38	0.01
DBP(mmHg)	84.41±14.82	81.83±14.80	83.86±17.36	82.84±16.02	83.52±15.98	Ns
Fat (% Body weight)	29.82±10.56	27.94±9.86	27.57±11.33	28.59±9.88	28.47±10.67	Ns
TBW (% Body weight)	57.21±8.40	56.26±7.73	57.95±10.09	56.49±8.10	57.22±8.94	Ns
ECFv (% Body weight)	26.03±3.42	26.17±4.29	27.09±4.44	25.37±3.55	26.37±4.04	0.01
ECFv/TBW	0.455±0.032*	0.467±0.046	0.464±0.047	0.449±0.024	0.460±0.040	0.01
S Glucose (mg/dl)	112.51±63.09	118.85±80.69‡	105.90±58.54	93.47±32.52	108.54±62.20	0.01
BUN (mg/dl)	113.20±37.39**	115.88±41.23	131.43±55.02	111.11±46.54	120.29±47.35	0.01
S Creatinine (mg/dl)	9.80±3.68**	11.66±3.81‡‡	9.40±3.75	9.27±3.32	9.91±3.77	0.01
Cholesterol (mg/dl)	185.75±42.72*‡‡	196.95±51.40‡‡	152.54±38.04	166.78±38.77	172.61±45.76	0.01
Triglycerides (mg/dl)	225.89±154.22‡‡	236.37±142.75‡‡	151.86±103.62	162.77±94.29	191.16±132.56	0.01
s Albumin (g/dl)	3.39±0.58**‡‡	3.78±0.55‡‡	4.12±0.53	4.32±0.51	3.86±0.65	0.01
TroponinT (ng/ml)	429.19±521.51	558.95±416.75	759.72±796.85	651.00±446.77	615.14±640.43	0.001
NT-proBNP (pg/ml)	17,181±27,914	12,455±17,092‡	21,778±28,000	14,636±15,979	17,893±25,252	0.01
CRP (mg/dl)	0.93±1.25‡‡	1.10±1.42‡	1.42±1.54	1.50±1.64	1.22±1.47	0.001

Values are expressed as mean ± SD. BMI, body mass index; W/H, waist to hip ratio; TBW, total body water; ECFv, extra cellular fluid volume; NT-proBNP, N-terminal fragment of B type natriuretic peptide; CRP, C-reactive protein; SBP, systolic blood pressure; DBP, diastolic blood pressure. *= p<0.05 vs APD; **= p<0.01 vs APD; ‡= p<0.05 vs HD; ‡‡= p<0.01 vs HD.

Also, Lacson showed that 38% of 65,000 participating patients in their study had Hb levels between 11-12 g/dL (Lacson et al., 2003). In the analysis made by Ebbenin United States Renal Data System (USRDS), the fluctuations on Hb levels over a period of 6 months were classified consistently in lower levels to 11.0 g/dL (low Hb group) between 11.0-12.5 g/dL (target Hb group) and greater than 12.5 g/dL (high Hb group). These results showed

Table 2. Availability of anemia evaluation test.

Test	Dialysis modality					
	CAPD	**APD**	**HD**	**HDs**	**Total**	**P**
Hemoglobin	77.8	80	75	83.7	78	Ns
Hematocrit	75.7	74.8	71.1	80.8	74.5	Ns
Ferritin	0	8.1	10.9	5.8	6.4	0.01
Iron	0	3.7	14.4	7.7	7.2	0.01
Transferrin	0	0	0	0	0	Ns
TSAT	0	0	0	0	0	Ns

Data are expressed as % into each group. P was calculated by x^2 test.

Table 3. Anemia evaluation tests in a centralized laboratory.

Test	Dialysis Modality					
	CAPD	**APD**	**HD**	**HDs**	**Total**	**p**
Hemoglobin (g/dL)	11.70±2.58	11.96±2.55	11.29±2.49	11.66±2.25	11.59±2.51	0.07
Hb<11 (%)	34.3	35.6	31.7	33.7	33.5	Ns
Hb>11, ≤13 (%)	40.9	33.3	44.7	42.3	41.2	
Hb>13 (%)	24.8	31.1	23.6	24	25.4	
Transferrin (mg/dL)	193.0±51.8	200.7±52.8	187.0±55.2	209.4±57.3	194.4±54.5	0.01
Serum Fe (µg/dL)	90.0|50.0	80.0|42.5	110.0|65.0	90.0|50.0	90.0|60	0.01
TSAT (%)	40.34|22.94**	33.71|23.05	46.04|41.42**	35.40|29.68	39.92|30.18	0.01
TSAT<20% (%)	8.7	18.5	7	16.3	10.9	0.01
TSAT>20%, ≥50% (%)	65.2	63	50	57.7	58	
TSAT>50% (%)	26.1	18.5	43	26	31.1	

Hb, hemoglobin; Serum Fe, serum iron; TSAT, Transferrin saturation; Serum Fe and TSAT are expressed as median and interquartile range. *= p<0.05 vs APD; **= p<0.01 vs APD.

that only 10% of patients maintained Hb levels in their initial classification during 6 months (Ebben et al., 2006). In our study, 67.3% of HD patients had Hb level ≥11 g/dL, while in The International Dialysis Outcomes and Practice Patterns Study (DOPPS) the same level was found in a range of 55%-77% (Pisoni et al., 2004). Furthermore, Hb level (11.4 g/dL) found in our study was coincidentally the same that was found in five European countries that participated in the DOPPS I study, while in the DOPPS II study, the results indicated that the Japanese patients had Hb lower levels than European and American patients, with values of 10.1%, 11.4% and 11.7%, respectively. Over time, there has been improvement in Hb levels in other European countries; however, DOPPS data also showed a substantial proportion of patients that do not achieved the Hb target ranges(Port et al., 2006).

Serum ferritin and TSAT are the standard laboratory tests to evaluate iron stores, and the limits for diagnosis of iron deficiency. Although these tests are used routinely to guide iron therapy in dialysis patients, studies have shown at ferritin and TSAT cutoffs for diagnosis of iron deficiency must be much higher than that used in the general population. In addition, studies that have administered intravenous iron to dialysis patients have found ferritin and TSAT repeatedly to be poorly predictive of hemoglobin responsiveness (Coyne et al., 2007). However, in this study, the ferritin was not measured in all

Table 4. Anemia management.

Test	Dialysis modality					
	CAPD	APD	HD	HDs	Total	p
Erythropoietin	13.5	28.1	29.9	28.3	23	0.01
Folic acid	42.6	40	35.9	26	37.3	0.05
Iron (any form)	30	34.8	15.2	23.1	24.7	0.02
Vitamin B (complex)	27.8	30.4	33.5	36	30.1	Ns
Transfusions (n)	1|3	1|2	3|4	3|4	2|3	0.01

Data are expressed as % into each group, except for transfusions (median and interquartile range). P was calculated by x2 test or Kruskal Wallis test.

Table 5. Univariate analysis of clinical and biochemical characteristics between survivor and non-survivor groups.

	Survivors			Non-survivors			Total			P
N			567			182			749	
Gender (F/M)	249	/	318	88	/	94	337	/	412	Ns
Diabetes (Y/N)	85.7		62.9	14.3		37.1	56.1		43.9	0.001
Age (yr)	45.81	±	17.69	57.70	±	13.70	48.70	±	17.56	0.001
Height (cm)	157.18	±	11.10	157.03	±	10.02	157.14	±	10.84	Ns
Weight (kg)	62.38	±	16.54	64.27	±	13.40	62.84	±	15.85	Ns
SBP (mmHg)	137.60	±	24.83	145.83	±	26.31	139.60	±	25.43	0.001
DBP(mmHg)	83.77	±	16.27	82.67	±	15.16	83.50	±	16.01	Ns
S Glucose (mg/dl)	100.79	±	49.79	133.27	±	86.61	108.66	±	62.30	0.001
BUN (mg/dl)	120.63	±	46.69	119.38	±	49.81	120.33	±	47.44	Ns
S Creatinine (mg/dl)	10.31	±	3.79	8.65	±	3.44	9.91	±	3.77	0.001
Cholesterol (mg/dl)	173.59	±	45.28	169.61	±	47.32	172.62	±	45.78	Ns
Triglycerides (mg/dl)	192.45	±	128.66	188.34	±	145.08	191.45	±	132.74	Ns
s Albumin (g/dl)	3.97	±	0.59	3.53	±	0.71	3.86	±	0.65	0.001
Ca (mg/dl)	9.19	±	1.02	9.02	±	1.00	9.15	±	1.02	0.054
Ca_{Alb} (mg/dl)	9.43	±	1.01	9.60	±	0.95	9.47	±	0.99	0.03
P (mg/dl)	5.67	±	2.09	5.12	±	2.09	5.54	±	2.10	0.003
PTH (pg/mL)	259.7	±	298.2	199.5	±	347.4	246.0	±	312.0	0.047
CRP (mg/dl)	1.02	±	1.30	1.85	±	1.76	1.22	±	1.47	Ns
Hemoglobin (g/dL)	11.7	±	2.5	11.1	±	2.5				
Hematocrit (%)	30.8	±	6.2	30.6	±	8.2				
Transferrin (mg/dL)	196.5	±	52.7	187.8	±	59.6				
Iron (mg/dL)	1.76	±	4.24	1.39	±	1.97				

Values are expressed as mean ± SD and as numbers. SBP, systolic blood pressure; DBP, diastolic blood pressure; PTH, Parathyroid hormone; Ca, Total serum calcium; Ca_{alb}, Calcium corrected for albumin; P, phosphorus; PTH, Parathyroid hormone; CRP, C-reactive protein.

patients and in none case TSAT was determined.

The anemia treatment is an important factor associated with prognoses, mortality, hospitalization and quality of life in dialysis patients (Pisoni et al., 2004). Many efforts are still needed to allow that a greater patient's proportion reaching the recommended Hb ranges. The results of the DOPPS study show the difficulties in implementing clinical guidelines in the everyday management of

individual patients (Locatelli et al., 2004). In same circumstances, our study provides real information and serves as a basic instrument for data about the implementation of clinical guidelines in routine clinical practice.

CONCLUSION

The CPGs have become the standard of efficiency most important to standardize and improve clinical practice. On our study, the results showed a low degree of adherence to international recommendations for the diagnostic and treatment of anemia. The frequency with which the target ranges were reached was far from the theoretical objectives, probably because for an inadequate guidelines knowledge, to lack of necessary resources for the patient's treatment or an inadequate monitoring of these parameters. We therefore recommend that future guidelines will come accompanied by educational interventions in the early diagnosis and treatment of disorders associated with CKD.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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