



Trabajo Original

Nutrición artificial

Patients with enteral nutrition at risk of refeeding syndrome show electrolyte abnormalities at admission in the Emergency Department

Pacientes con nutrición enteral en riesgo de desarrollar síndrome de realimentación presentan trastornos electrolíticos al ingreso en el Servicio de Urgencias

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Abstract

Introduction: refeeding syndrome (RFS) is a metabolic complication in the initial phase of nutritional therapy (NT). Studies evaluating electrolyte abnormalities among patients at risk for RFS undergoing NT in the Emergency Department (ED) are scarce.

Objective: to explore the occurrence of electrolyte abnormalities among patients at risk for RFS with enteral nutrition admitted to the ED.

Material and methods: a retrospective cohort study that evaluated 440 adult patients undergoing NT, admitted to the ED of a public tertiary teaching hospital regarding RFS risk. Additional eligibility criteria included nutritional assessment by registered dietitians and at least one dose of an electrolyte (sodium, potassium, magnesium, phosphate, calcium) ordered by physicians. Differences were considered statistically significant at $p < 0.05$.

Results: RFS risk criteria identified 83 (18.9 %) (65.1 % elderly, aged 64.2 ± 11.6 years, 65.1 % male; body mass index, 17.3 ± 3.5 kg/m²) patients at risk, of which 25 (30.1 %) had phosphorus, 48 (57.8 %) magnesium, and 60 (72.3 %) calcium dosages within the first week. All patients at risk for RFS had potassium and sodium evaluations. In those patients where serum levels were checked, hypophosphatemia was identified in 10 (40.0 %), hypomagnesemia in 12 (25.0 %) and hypokalemia in 13 (15.7 %) patients. Almost half of phosphorus assessments resulted from advice by registered dietitians to the staff.

Conclusion: electrolyte evaluation was not ordered in all at-risk patients on NT. Despite the small sample, hypophosphatemia was a very common condition among this group. This study highlights the importance of RFS risk screening awareness among NT patients, and the important role of registered dietitians in this context. Larger sample studies are needed to confirm these results.

Keywords:

Nutritional therapy.
Nutritional support.
Refeeding syndrome.
Emergency department.
Hypophosphatemia.
Malnutrition.

Resumen

Introducción: el síndrome de realimentación (SR) es una complicación metabólica de la fase inicial del soporte nutricional (SN). Los estudios que evalúan trastornos electrolíticos en pacientes con riesgo de desarrollar SR y sometidos a NT en el servicio de Urgencias (SU) son escasos.

Objetivo: explorar la aparición de trastornos electrolíticos en pacientes con riesgo de desarrollar SR con nutrición enteral, ingresados en Urgencias.

Material y método: cohorte retrospectiva que evaluó 440 pacientes adultos con SN ingresados en el SU en cuanto al riesgo de desarrollar SR. Los criterios de elegibilidad fueron una evaluación nutricional por dietistas y al menos una dosis de un electrólito (sodio, potasio, magnesio, fosfato, calcio) a petición de los médicos.

Resultados: se identificaron 83 (18,9 %) pacientes con riesgo (65,1 % ancianos, edad de $64,2 \pm 11,6$ años, 65,1 % de varones; índice de masa corporal, $17,3 \pm 3,5$ kg/m²), de los que 25 (30,1 %) habían recibido dosis de fósforo, 48 (57,8 %) magnesio y 60 (72,3 %) calcio. Todos los pacientes tenían evaluaciones de potasio y sodio. Entre los pacientes en los que se midieron niveles séricos, se encontró hipofosfatemia en 10 (40,0 %), hipomagnesemia en 12 (25,0 %) e hipopotasemia en 13 (15,7 %). Aproximadamente, la mitad de las evaluaciones de fósforo se llevaron a cabo por consejo de los nutricionistas al personal médico.

Conclusión: no se ordenó la evaluación de electrólitos en todos los pacientes con riesgo de SR en SN. A pesar de la pequeña muestra, la hipofosfatemia fue una condición muy común en este grupo. Este estudio destaca la importancia de la concienciación sobre el cribado del riesgo de SR en los pacientes con SN y el importante papel de los nutricionistas en este contexto. Se necesitan estudios con muestras grandes para confirmar estos resultados.

Palabras clave:

Terapia nutricional.
Soporte nutricional.
Síndrome de realimentación.
Urgencias.
Hipofosfatemia.
Desnutrición.

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INTRODUCTION

Refeeding syndrome (RFS) consists of metabolic changes that can occur on the reintroduction of nutrition in those who are malnourished or starved or in fasting state periods, and its occurrence mostly happens within the first 72 hours of nutritional therapy (NT) onset (1). It is characterized by an imbalance of electrolytes, mainly phosphate, potassium, magnesium, and calcium, and by vitamin disturbances, which can lead to impaired organ functioning (2,3). Data from the literature suggest a tendency to high mortality in this population, especially among malnourished, older, HIV, and critically ill patients (2,4,5).

RFS incidence largely ranges from 0 % to 80 % according to the definition used and the population studied (2). Clinical, biochemical, and nutritional criteria allow early identification of the risk for RFS, and considering that electrolyte shifts occur in the first 3 days after NT initiation, it is recommended to monitor electrolytes during this period (1,3,4,6). This metabolic condition should be screened and monitored closely, although some studies have suggested that health professionals may be unaware of RFS (3,7).

A slow initiation and titration of NT calories, correction of phosphate and other electrolyte imbalances, and thiamine supplementation represent the first steps in the appropriate treatment of RFS (3,4,8,9). Registered dietitians rely on physicians to order and monitor electrolytes, and to prescribe vitamins and electrolytes supplementation during NT.

Considering that enteral nutrition is a known risk factor for RFS, and that the Emergency Department (ED) is often the entryway into tertiary health services, our aim was to explore the occurrence of electrolyte disturbances in patients at risk for RFS with enteral nutrition who are admitted to the ED.

MATERIAL AND METHODS

STUDY POPULATION AND SAMPLE

This retrospective cohort study explored the medical records of adult patients undergoing enteral nutrition (exclusive or combined with oral feeding), admitted to the ED of a public tertiary teaching hospital from December 2017 to November 2018.

Patients could be already undergoing or initiating enteral nutrition in the ED. Additional inclusion criteria consisted of a nutritional assessment by a registered dietitian and at least one dosage of any of the following electrolytes — sodium, potassium, magnesium, calcium, or phosphorus — during ED hospitalization. Patients were excluded due to insufficient anthropometric and biochemical data, presence of cerebral palsy (NT chronically prescribed) or hospitalization < 24 hours. Considering the profile of the ED evaluated, that only rarely attends to patients undergoing parenteral nutrition, this subset of nutrition therapy was not evaluated in this study. The follow-up was done until hospital death or hospital discharge.

VARIABLES

Clinical and socio-demographic data were collected from the patients' medical records and consisted of age, sex, ethnicity, Quick Sequential Organ Failure Assessment (qSOFA) score, comorbidities, and admission diagnosis (10). The risk of RFS was identified according to institutional protocols for enteral nutrition, starting and advancing based on NICE guidelines (Fig. 1). After nutritional assessment and during enteral nutrition implementation, registered dietitians suggested electrolyte monitoring through electronic records. All biochemical assessments were ordered by ED physicians.

Electrolyte data were extracted from electronic records and included: sodium, potassium, magnesium, calcium, phosphorus, and albumin. The lower electrolyte cutoff values were: sodium < 136 mEq/L, potassium < 3.5 mEq/L, magnesium < 2.6 mg/dL, calcium < 8.8 mg/dL, and phosphorus < 2.5 mg/dL. Severe hypophosphatemia (HP) was classified when phosphorus < 1.5 mg/dL, moderate HP when 1.5 to 2.2 mg/dL, and mild HP when 2.2 to 2.4 mg/dL. Hypoalbuminemia was considered when albumin < 3.5 g/dL. Information regarding clinical outcomes consisted of ED and in-hospital length of stay (LOS) and mortality.

Given the retrospective observational nature of this study, nutritional protocols were not modified. All patients undergoing NT admitted to the ED were evaluated by registered dietitians and had anthropometric data measured or estimated (weight, height, and nutritional history) and recorded in electronic records. Body weight was measured with hospital light clothing and no shoes using a digital weighing scale balance (Lider®) to the nearest 0.1 kg, and height with a stadiometer (Lider®) accurate to 0.1 cm.

The patient has one or more of the following:
<ul style="list-style-type: none"> – BMI less than 16 kg/m² – Unintentional weight loss greater than 15 % within the previous 3-6 months – Very little nutritional intake for longer than 10 days – Low levels of potassium, phosphate or magnesium prior to feeding
Or the patient has two or more of the following:
<ul style="list-style-type: none"> – BMI less than 18 kg/m² – Unintentional weight loss greater than 10 % within the previous 3-6 months – Very little nutritional intake for longer than 5 days – A history of alcohol abuse or drugs including insulin, chemotherapy, antacids or diuretics (interpret with caution)
The patient has either of the following:
<ul style="list-style-type: none"> – BMI less than 14 kg/m² – Negligible intake for greater than 15 days

Figure 1.

Criteria for risk of refeeding syndrome according to NICE. (BMI: body mass index).

When anthropometric data were not possible to be measured, equations were used to predict body weight and height (11,12). For this study's purpose, the nutritional data that were extracted consisted of weight (kg), height (cm), history of unintentional weight loss and nutritional intake reduction, and oral intake during ED hospitalization. Body mass index (BMI) was calculated ($\text{weight} / [\text{height}]^2$) and classified according to age (13).

STATISTICAL ANALYSIS

Sample size was estimated based on an incidence of HP at 31.5 % in patients undergoing NT according to López et al. (2017), with an alpha value of 0.05 and a power of 80 %, which resulted in 83 patients (15). The Shapiro-Wilk test was used to evaluate the distribution of the variables. Normal distribution variables were expressed as mean \pm standard deviation, and non-normal distribution variables as median (P25-P75). For nominal variables, absolute and relative frequencies were expressed (n [%]). To compare means and medians, the independent samples t-test and Wilcoxon-Mann-Whitney test were used, respectively. Missing data were addressed with exclusion cases. Differences were considered statistically significant at $p < 0.05$. The statistical analysis was performed using the SPSS version 25 package.

ETHICS

This study was conducted according to the Declaration of Helsinki guidelines, and all procedures involving patients were approved by the institutional ethics committee (#18 – 0285). The authors signed an agreement to preserve patient and staff anonymity as related to the use of these data. The STROBE statement was used to organize and report the results (14).

RESULTS

Over the study period 465 patients received NT and were evaluated by registered dietitians. After exclusions (6 due to < 24 hours of hospitalization; 11 due to incomplete medical records, and 8 due to cerebral palsy), 440 patients were evaluated, as shown in the flowchart of study inclusion in figure 2. RFS risk criteria were applied and identified 83 (18.9 %) patients at risk (65.1 % elderly, 64.2 ± 11.6 years, 65.1 % male; BMI, 17.3 ± 3.5 kg/m²; 22 (26.5 %) in-hospital mortality cases). The patients' socio-demographic, clinical, and nutritional characteristics are described in table I.

According to the NICE (1) RFS risk criteria, 36 (43.4 %) patients had BMI < 16 kg/m², 33 (39.8 %) unintentional weight loss greater than 15 % within the previous 3 to 6 months, 2 (2.4 %) very little nutritional intake for more than 10 days, and 13 (15.7 %) low electrolyte levels prior to feeding initiation. Moreover, 27 (32.5 %) had BMI < 18.5 kg/m², 20 (24.1 %) unintentional weight loss greater than 10 % within the previous 3 to 6 months, 34 (41 %) very little nutritional intake for longer than 5 days, and 14 (16.9 %)

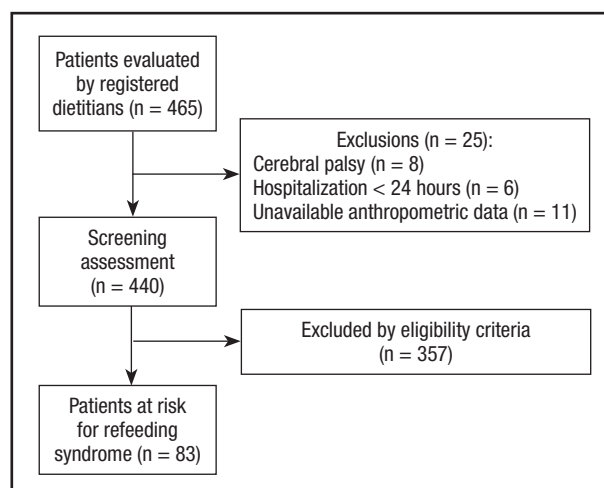


Figure 2.

Flowchart of study inclusion.

Table I. Patient socio-demographic and clinical characteristics (n = 83)

Characteristics	Values
Age, yrs	64.2 \pm 11.6
Sex, male, n (%)	54 (65.1)
Ethnicity, n (%)	
White	66 (79.5)
Black	12 (14.5)
Other	5 (6.0)
Admission diagnosis, n (%)	
Respiratory	32 (38.6)
Gastrointestinal	28 (33.7)
Neurological	10 (12.0)
Cardiovascular	3 (3.6)
Renal	3 (3.6)
Other	7 (8.4)
qSOFA \geq 2 criteria, n (%)*	24 (32.0)
Weight (kg)	47.3 \pm 11.8
BMI, kg/m ²	17.3 \pm 3.5
Overweight (\geq 25.00)	2 (2.4)
Normal (18.5 to 24.99)	22 (26.5)
Mild underweight (17 to 18.49)	13 (15.7)
Moderate underweight (16 to 16.99)	13 (15.7)
Severe underweight (< 16.00)	33 (39.8)
Albumin, mg/dL	3.05 \pm 0.59
Intravenous glucose solutions, n (%)	45 (54.2)
LOS in ED, d	5.9 \pm 2.9
LOS in Hospital, d	12 (7-18)

BMI: body mass index; ED: emergency department; LOS: length of stay; qSOFA: Quick Sequential Organ Failure Assessment. Data expressed as n (%); mean \pm SD; median (P25-P75). *Patients with two or more qSOFA criteria (n = 75).

Table II. Biochemical characteristics of patients during the first week of hospitalization

Electrolytes	Electrolyte assessment within the first 7 days, n (%)	Biochemical alterations, n (%)	Lowest serum levels of biochemical alterations
Phosphorus, mg/dL	25 (30.1)	10 (40.0)	1.49 ± 0.66
Magnesium, mg/dL	48 (57.8)	12 (25.0)	1.38 ± 0.12
Potassium, mEq/L	83 (100.0)	13 (15.7)	3.06 ± 0.23
Sodium, mEq/L	83 (100.0)	46 (55.4)	132 ± 2.9
Calcium, mg/dL	60 (72.3)	38 (63.3)	8.12 ± 0.38

Data expressed as n (%); mean ± SD.

Table III. Comparison between the hypophosphatemia (HP) and non-hypophosphatemia (non-HP) groups

Characteristics	HP group (n = 10)	Non-HP group (n = 15)	p-value
Age, years	67 ± 8	62 ± 12	ns
BMI, kg/m ²	17.4 ± 3.8	15.5 ± 3.2	ns
Albumin, g/dl	2.8 ± 0.4	3.0 ± 0.5	ns
qSOFA ≥ 2 criteria, n (%)	3 (33.3)	3 (21.4)	ns
LOS at ED, d	5 ± 2	7 ± 3	ns
LOS in hospital, d	13 (10-27)	15 (12-24)	ns

BMI: body mass index; ED: emergency department; LOS: length of stay; qSOFA: Quick Sequential Organ Failure Assessment. Data expressed as n (%); mean ± SD; median (P25-P75). *Evaluation by qSOFA in the HP group (n = 9) and non-HP group (n = 14).

a history of alcohol abuse or medication use including insulin, chemotherapy, antacids, or diuretics.

In the overall sample, 44 (53 %) patients were already undergoing enteral nutrition prior to entering the ED, and the others started at the time of admission. The patients' biochemical characteristics in the first week of hospitalization are presented in Table II. Phosphorus alteration was observed in 10 (40.0 %), on which 4 (40.0 %) were classified as severe HP, 4 (40.0 %) as moderate HP, and 2 (20.0 %) as mild HP. Albumin was evaluated in 47 (56.6 %) patients and hypoalbuminemia was present in 34 (72.3 %) individuals. Of electrolyte assessments 42.2 % resulted from advice by registered dietitians to the staff.

Comparing the HP and non-HP groups no differences were observed in relation to age, BMI, albumin serum levels, ED, and hospital LOS. Malnutrition was more prevalent among non-HP subjects (14 (93.3 %) than in the HP group 6 (60.0 %) (Table III). A tendency to higher mortality in the HP group compared to the non-HP group was identified (3 [30.0 %] vs. 2 [13.3 %]), although it was not statistically significant. Regarding suspected infection screening, a qSOFA score ≥ 2 was observed in 24 (32.0 %) patients. Analyzing those with phosphorus dosing, the ones with a qSOFA ≥ 2 had more HP when compared to those with a qSOFA < 2 (3 [50.0 %] vs. 6 [35.3 %]).

When comparing the results by age group, the mean ages of the elderly and adults were 70.4 ± 8.2 vs 52.5 ± 7.2 years

(p < 0.001); unintentional weight loss in the last 3 to 6 months was present in 52 (96.3 %) vs 27 (93.1 %) patients, with actual body weight being 46.2 ± 10.7 vs 49.4 ± 13.6 kg, unintentional weight loss 14.6 (10.2 to 26.5) vs 15.3 (8.6 to 27.6) % and BMI 17.3 ± 3.5 vs 17.2 ± 3.6 kg/m², of which 22 (40.7 %) vs 11 (37.9 %) were severely malnourished, respectively. Median ED LOS was 5.0 (3.0 to 6.5) vs 6.0 (5.0 to 8.0) days, and in-hospital LOS was 12.0 (6.0 to 21.3) vs 12.0 (8.5 to 16.0) days. A statistically significant difference in ED LOS was observed, it being lower in the elderly group (p = 0.026).

During the first week after admission both the elderly and adults showed, respectively, altered serum levels of sodium (30 [55.6 %] vs 16 [55.2 %]), potassium (11 [20.4 %] vs 2 [6.9 %]), magnesium (9 [30.0 %] vs 3 [16.7 %]), phosphorus (8 [44.4 %] vs 2 [28.6 %]), calcium (24 [60.0 %] vs 14 [70.0 %]), and albumin (24 [77.4 %] vs 10 [34.5 %]), but no statistical significance was observed.

DISCUSSION

Almost one fifth of patients on NT admitted to the ED were identified as at risk for RFS. HP was identified as a very common condition, despite the small size of the sample analyzed. In spite of their key role in the management of RFS, phosphorus and

magnesium tests were ordered in only one third and two thirds of at-risk patients, respectively, which suggests awareness is low among ED staffers regarding this condition, even after receiving advice by a registered dietitian.

NICE guidelines suggest criteria for the identification of patients at risk of RFS. RFS definitions are wide-ranging, and some studies only rely on electrolyte disturbances, considering phosphorus values a major criteria for RFS when decreases from baseline $> 30\%$ or levels < 0.60 mmol/L are identified (1,3,4,6,8,9). In our sample, 18.9 % of patients were considered to be at risk for RFS. In contrast, a study found about 54 % of internal medicine patients were at risk for developing RFS, of which 14 % actually developed the syndrome based on phosphorus levels (16). Another study with patients receiving enteral nutrition showed that 51.9 % of patients were at risk of RFS (15). Pourhassan et al. (2017) demonstrated that 239 (69.9 %) of their older inpatients were at risk for RFS by applying the NICE criteria, and 51 (14.9 %) had HP as a hallmark of RFS (17).

López et al. (2017) evaluated hospitalized patients with enteral feeding and found a high HP incidence of 31.5 % with severe HP at 1.1 %; however, around 51 % of patients were at risk of developing RFS, whereas in our sample of at-risk patients about 10 (40 %) developed HP, and 4 (40 %) developed severe HP (15). Another study that evaluated 2307 elderly inpatients identified HP in 14.1 %, and severe HP in 4.1 %; and when the HP group was compared to the non-HP group, the former received significantly more enteral feeding: 39.7 % vs 12.8 % ($p < 0.0001$) (18). Parenteral nutrition seems to be a risk factor for RFS (4,8). A study analyzed the risk of RFS in patients receiving parenteral nutrition and identified 30.0 % of HP and 27.5 % of hypokalemia and hypomagnesemia (19).

Sepsis is a known risk factor for RFS, and in the study of Kagansky et al. (2005) elderly patients with HP had a threefold higher presence of sepsis than patients without HP (33.2 % vs 11.7 %, $p < 0.0001$), respectively (18). Nevertheless, the presence of sepsis or infection was similar between internal medicine patients with and without risk of RFS (16). In our study, 32.0 % of patients had a positive qSOFA screening score and the presence of HP showed a tendency to be higher in those patients.

Studies suggest that RFS contributes to higher mortality especially in specific populations (2,4,5). The overall mortality in our study was 22 (26.5 %). Due to our small sample we did not perform an adjusted analysis. Kagansky et al. (2005) identified that older patients with HP showed a threefold increased mortality when compared to non-HP patients, but HP was not an independent risk factor for mortality (18).

After a RFS diagnosis one of the management steps to reduce clinical outcomes is to reduce calorie intake (6). A single-blinded controlled trial in critically ill adults showed that caloric restriction, compared to standard treatment, during the management of RFS contributed to increase overall survival time (48.9 ± 1.46 vs 53.65 ± 0.97 , $p = 0.002$), respectively (20). In a similar way, a study showed that patients at RFS risk who received $< 50\%$ of their caloric target had a reduced 6-month mortality rate when compared to standard practice (21). We agree that this is an

important piece of data to consider when analyzing clinical outcomes, but we did not evaluate such data considering the primary outcome of this study.

It is recommended that patients at risk for refeeding syndrome have electrolyte assessments, preferably within the first 72 hours after NT onset (3,4,6,8,9). Despite the prevalence of RFS risk, Janssen et al. (2019) demonstrated that physicians and fifth-year medical students are unaware of RFS, when only 14 % ($n = 40$) of them were able to correctly diagnose a case vignette of RFS (7). This low awareness about RFS may have contributed to the reduced phosphorus and magnesium assessments seen in the first week after admission in the ED.

To our knowledge, this is the first study to specifically evaluate RFS in patients undergoing enteral nutrition admitted to an ED; despite this fact, we have some limitations. We tried to be as pragmatic as possible in evaluating the awareness of this condition and assessing the existing data regarding biochemical monitoring in patient records. As a result of this, we had the limitation of having a small sample of patients with electrolyte measures, specifically phosphorus evaluations (1). Also, we were not able to perform a multivariate analysis for clinical outcomes due to sampling issues regarding the exclusions of missing data (biochemical characteristics) (2). We did not analyze NT protein-calorie adequacy during the first week after admission to the ED due to a lack of NT data in the patients' electronic records (NT data were registered in printed forms not consulted in the present study) (3). Additionally, phosphorus testing on a day-by-day basis was not possible due to a low frequency of assessments (4). Due to the ED profile, in which patients undergoing parenteral nutrition are rarely attended to, this subset of nutrition therapy was not evaluated in this study. Despite these limitations, we believe that our results reflect the local ED reality, but possibly fail to achieve external generalization because of a loss of statistical power due to missing data.

CONCLUSION

Electrolyte assessments were not ordered in all patients at risk for RFS on NT. Almost half of phosphorus assessments resulted from advice by registered dietitians. HP was a very commonly condition among at-risk patients undergoing NT at the ED. This study highlights the importance of RFS risk screening awareness concerning NT patients, and the important role of registered dietitians in this context. Large-sample studies are needed to confirm and to expand the potential for generalization of our results.

AUTHOR CONTRIBUTIONS

R.S.P and O.S.F equally contributed to the conception, design, acquisition, analysis, and interpretation of the study. R.S.P and O.S.F drafted the manuscript and critically revised it. Both authors gave their final approval and agreed to be fully accountable for ensuring the integrity and accuracy of this work.

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