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ORIGINAL RESEARCH REPORT

Serum Electrolyte and Metabolic Changes During Conditioning of Autologous Hematopoietic Stem Cell Transplantation in Patients with Autoimmune Diseases: A Prospective Study in a Single Institution

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Abstract

Background and objectives: **A hematopoietic stem cell transplant (HSCT) includes a conditioning regimen which may cause unwanted metabolic changes. We analyzed the changes in electrolytes, glucose, urea, and glomerular filtration rate in patients with multiple sclerosis (MS) who underwent an autologous HSCT employing the "Mexican method."**

Patients and methods: **Serum and urinary electrolytes, blood glucose, creatinine, uric acid, and estimated glomerular filtration rate (eGFR) were prospectively assessed on days −11, −9, and 0 in a group of 75 patients with MS receiving an autologous HSCT employing the "Mexican method," which includes high doses of both cyclophosphamide (Cy, 200 mg/kg) and rituximab (1000 mg).**

Results: **The median age of the patients was 46 years, with a range of 20−65. Baseline data were defined at day −11 of the HSCT. There were significant changes in serum and urinary electrolytes, which diminished substantially after the delivery of high-dose Cy; 12 patients (16%) developed hyponatremia and 2 had hyponatremia-induced seizures, which resulted in hospital admissions. A comparison of baseline blood metabolites with those obtained after the full Cy dosage (day 0) revealed a significant increase in blood glucose and uric acid levels with an associated decrease in serum calcium, sodium, and potassium levels. The salient findings were drug-induced hyponatremia and hyperglycemia.**

Conclusion: **Significant changes in serum electrolytes, blood glucose, creatinine, uric acid, and estimated glomerular filtration rate (eGFR) were observed in patients given autologous HSCT for MS employing high-dose Cy. Some of these changes may have clinical consequences, mainly those derived from iatrogenic hyponatremia. No evidence of damage to renal function was observed at day 0.**

Keywords: Serum electrolyte, Auto-HSCT, Autoimmune diseases

1. Introduction

Autologous hematopoietic stem cell transplants **(HSCTs)** for multiple sclerosis **(MS)** require a conditioning regimen that may result in unfavorable metabolic changes. Most conditioning regimens for autologous HSCT in MS employ a high dose of cyclophosphamide (Cy) combined with other immunosuppressive agents, such as antithymocyte globulin [1], rituximab [2], fludarabine [3] and others [4]. Since 2015, we have been employing the combination of a high dose of Cy with rituximab [5], and we have been able to graft over 1300 MS patients, following the protocol that we have established as the "Mexican method" [6]. Our

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conditioning regimen includes the administration of 200 mg/kg cyclophosphamide, in two blocks, with a 7-d interval and a period of mobilization with filgrastim lasting 8 d. It is entirely ambulatory; that is, patients are transported to the center for evaluation or to undergo procedures. The most observed side effects of the conditioning regimen are electrolyte and other metabolite abnormalities that may destabilize the patient to the point of requiring hospitalization. In this study, we report the changes observed in electrolytes, glucose, urea and glomerular filtration rate in a group of MS patients who underwent autologous HSCT employing the "Mexican method".

2. Patients and Methods

2.1. Patients

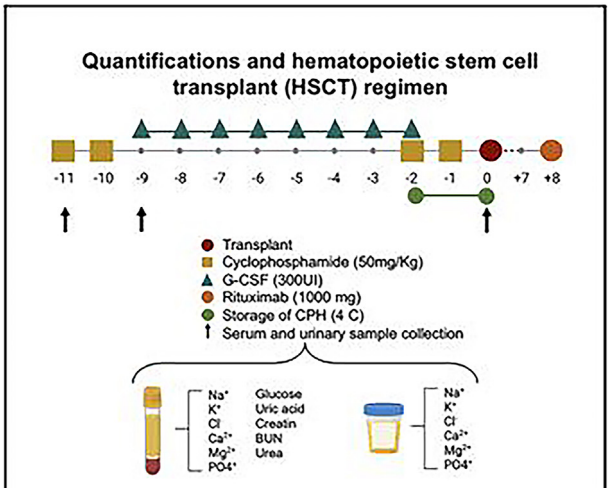
Consecutive patients with MS referred to our center for a HSCT between February and September 2021 were prospectively included in the study; 75 participants were accrued, 70 (93.3%) of whom had MS and 5 (6.6%) had chronic inflammatory demyelinating polyneuropathy. Relapsing-remitting (RRMS), secondary-progressive (SPMS), and primary-progressive (PPMS) cases of MS were included if their Karnofsky performance status was above 70% and their expanded disability status scale (EDSS) score was 8 or below in the 2 weeks prior to transplantation [7,8]. None of the patients had received myelotoxic agents prior to inclusion in the study and all had normal complete blood cell counts when cellular mobilization was begun. All patients underwent a washout period of at least three months for other immunosuppressive agents. The pre-transplant EDSS score assessment was done by the same neurologist. The study was approved by the Ethics Committee of the Clínica RUIZ (*Conbioetica* 21CEI00120130605, Registry No. 13 CEI 21 114 126). All patients signed a consent form after being fully informed on the procedure's benefits and potential complications. The protocol is registered in *ClinicalTrials.gov,* identifier NCT02674217.

2.2. Peripheral blood stem cell mobilization and apheresis

PBSC mobilization was conducted with Cy and filgrastim (G-CSF) [6–9]. Intravenous Cy (50 mg/kg) was administered in a 120-min period on days −11 and −10. Subcutaneous G-CSF (10 μg/kg/bid) was given on days −9 to −1. Using either a peripheral vein or a Mahurkar-type subclavian catheter, the apheresis procedure was performed on day −2, using an *Amicus* (*Fresenius Kabi*, Deerfield, IL, USA) or a *Spectra Optia* machine (*Terumo BCT*, Lakewood, CO, USA), following the Spin-Nebraska protocol [10]. The goal of the apheresis is to obtain at least 1×10^6 viable CD34+ cells/kg for each patient. CD34+ cell levels in peripheral blood were not measured prior to the apheresis procedures.

2.3. Conditioning and autografting

After collecting the required number of peripheral blood CD34+ cells, intravenous Cy (50 mg/kg) was administered over a 120-min period on day −2, followed by MESNA (1000 mg/m^2 over a 180-min period), ondansetron 8 mg, dexamethasone 4 mg, and pantoprazole 40 mg, all on an outpatient basis. The cumulative dose of Cy was 200 mg/kg. Fig. 1 summarizes these data. After the intravenous Cy,



Female	56% (42)
Male	44% (33)
Age (yrs.)	46 (20-65)
Weight (kg)	73.3 (44-135)
Height (cm)	173 (150-194)
BMI (Kg/m^2)	24.9 (17.2-47.5)
Diagnosis	
Multiple sclerosis	70
Inflammatory polyneuropathy	5

Fig. 1. HSCT protocol following the "Mexican Method."

ondansetron (4 mg every 12 h after chemotherapy), oral cotrimoxazole (800/160 mg every 24 hours), oral fluconazole (200 mg), and oral acyclovir (400 mg every 12 hours) were used in all patients until granulocyte levels increased above 0.5 × 10^9/L. Throughout this period, a complete clinical examination and full laboratory work-up were performed on all patients every 48 hours. After granulocyte recovery, a single high dose of rituximab (1000 mg) was administered over a 3-h period. To prevent infections in the following 6 months, we prescribed cotrimoxazole 800/160 mg bid three times a week, acyclovir 800 mg daily, and rituximab (100 mg) every 2 months over a 12-months period. The informed consent decision to receive rituximab therapy despite known John Cunningham virus antigenemia was signed by each individual.

2.4. Apheresis product preservation, studies, and infusion

We kept 1 mL aliquots of the products of apheresis in ACD-A (*Baxter Healthcare*, Deerfield, IL, USA) at 4 °C in 1000 mL transfer packs (*Baxter Healthcare*) made of gas impermeable polyvinyl chloride plastic film for up to 96 hours. Total white mononuclear cells (MNC) and CD34+ cell counts were obtained by flow-cytometry in an *EPICS Gallios* system (*Coulter Electronics*, Hialeah, FL, USA) using phycoerythrin-labeled anti-CD34 HPCA-2 monoclonal antibody (*Becton Dickinson*, San José, CA, USA) and a fluorescein isothiocyanate tagged anti-CD45 monoclonal antibody (*Beckman Coulter, Hialeah, FL, USA*) gating in 7'amino-actinomycin-D-excluding cells [10]. Stored MNC viability studies were conducted by propidium iodide exclusion in a flow cytometer. The apheresis products obtained on day −2 were reinfused into the patients on days 0 and + 1, respectively, after storage in a conventional blood bank refrigerator (*Thermoforma*, Marietta, OH, USA).

2.5. Serum and urine studies

Serum and urine samples were collected on day −11 before initiating the regimen, on day −9 before the delivery of filgrastim, and on day 0 before the reinfusion of CD34+ cells. Sodium, chloride, potassium, and calcium were measured by indirect potentiometry, with selective and reference electrodes [11]. Uric acid, magnesium, and phosphorus were measured by absorbance, and glucose, urea, blood urea nitrogen (BUN), and creatinine were measured with a kinetic method [12]. Ionized calcium was determined with the formula:

$$Ca^{++} = \frac{\left[(measured\ Ca \times 6) - \left(\frac{Total\ protein}{3}\right)\right]}{Total\ protein + 6}$$

The glomerular filtration rate was calculated with the chronic kidney disease-epidemiology collaboration (CKD-EPI) formula [13]. Osmolarity was determined based on the glucose, urea, and sodium values. All clinical laboratory methods are accredited by the *Entidad Mexicana de Acreditación* to guarantee the reproducibility and reliability of all results [14].

2.6. Statistical analysis

The Kolmogorov–Smirnov test was used to evaluate the normality of the distribution of the data to be analyzed. Most of the parameters in our study did not conform to a normal distribution; hence, repeated measures comparisons were analyzed with Friedman's test, whereas Wilcoxon's test was used to evaluate between-group differences [15]. Results with P values < 0.05 were considered statistically significant. Statistical analysis was performed using SPSS 25 software (IBM Corp. Published 2017. IBM SPSS Statistics for Windows, version 25.0, Armonk, NY, USA) and GraphPad Prism 9 (GraphPad Prism version 9 for Windows, GraphPad Software, San Diego, CA, USA, www.graphpad.com).

3. Results

The study had a prospective enrollment of seventy five patients, the median age being 46 years, with a range of 20–65 (Table 1). The indications for HSCT were MS in 70 cases (93.3%) and chronic inflammatory demyelinating polyneuropathy in 5 (6.3%). When comparing baseline data (day −11) with the data obtained after the first Cy dose block (day −9), we observed a statistically significant decrease in serum urea, BUN, sodium, and chloride; whereas in urine, a statistically significant increase in urinary volume and a statistically significant decrease in sodium, potassium, and chloride were found.

Table 1. General characteristics of the patients studied

Characteristic and measure	
Female	56% (42)
Male	44% (33)
Age (yrs.)	46 (20–65)
Weight (kg)	73.3 (44–135)
Height (cm)	173 (150–194)
BMI (kg/m^2)	24.9 (17.2–47.5)
Diagnosis	
Multiple sclerosis	70
Inflammatory polyneuropathy	5

A comparison of the data obtained on day −11 with those obtained on day 0 revealed a statistically significant increase in glucose and uric acid with an associated decrease in sodium and potassium. These differences in serum levels are summarized in Fig. 2 and detailed in Supplementary Tables S1-S3. In urine samples, the variables that differed from baseline were sodium, potassium, chloride, and the urinary output. These differences are summarized in Supplementary Tables S4-S5. The sodium and potassium levels in serum and urine are presented in Figs. 2 and 3, respectively.

The eGFR measurement was performed on days −11, −9, and 0, and we found no statistically significant differences between these measurements. These results are shown in Fig. 4. When analyzing serum electrolyte abnormalities, we observed that at day 0, 16% (n = 12) of patients presented isotonic hyponatremia, 38.6% (n = 29) hypokalemia, 95.6% (n = 71) hypocalcemia, 13.3% (n = 10) hyperglycemia, and 21.3% (n = 16) hyperuricemia. On day −11, only one patient had hyponatremia (134.4); on day −9, 20 patients had hyponatremia, (10 patients had levels between 130 and 135 and 10 had levels between 120 and 129); and on day 0, all 12 patients with hyponatremia had levels between 130 and 135. Three patients who had hyponatremia on day −9 continued to exhibit hyponatremia on day 0 (patient 1: 129.3 mEq−134.4 mEq, patient 2: 128.4 mEq−134.8 mEq, and patient 3: 134.2 mEq−134.1 mEq). All electrolyte abnormalities found are shown in Table 2.

4. Discussion

Cy is an alkylating agent used in the treatment of hematological neoplasms, some autoimmune diseases, and as part of the conditioning regimen administered before HSCT. At high doses, it is a potent

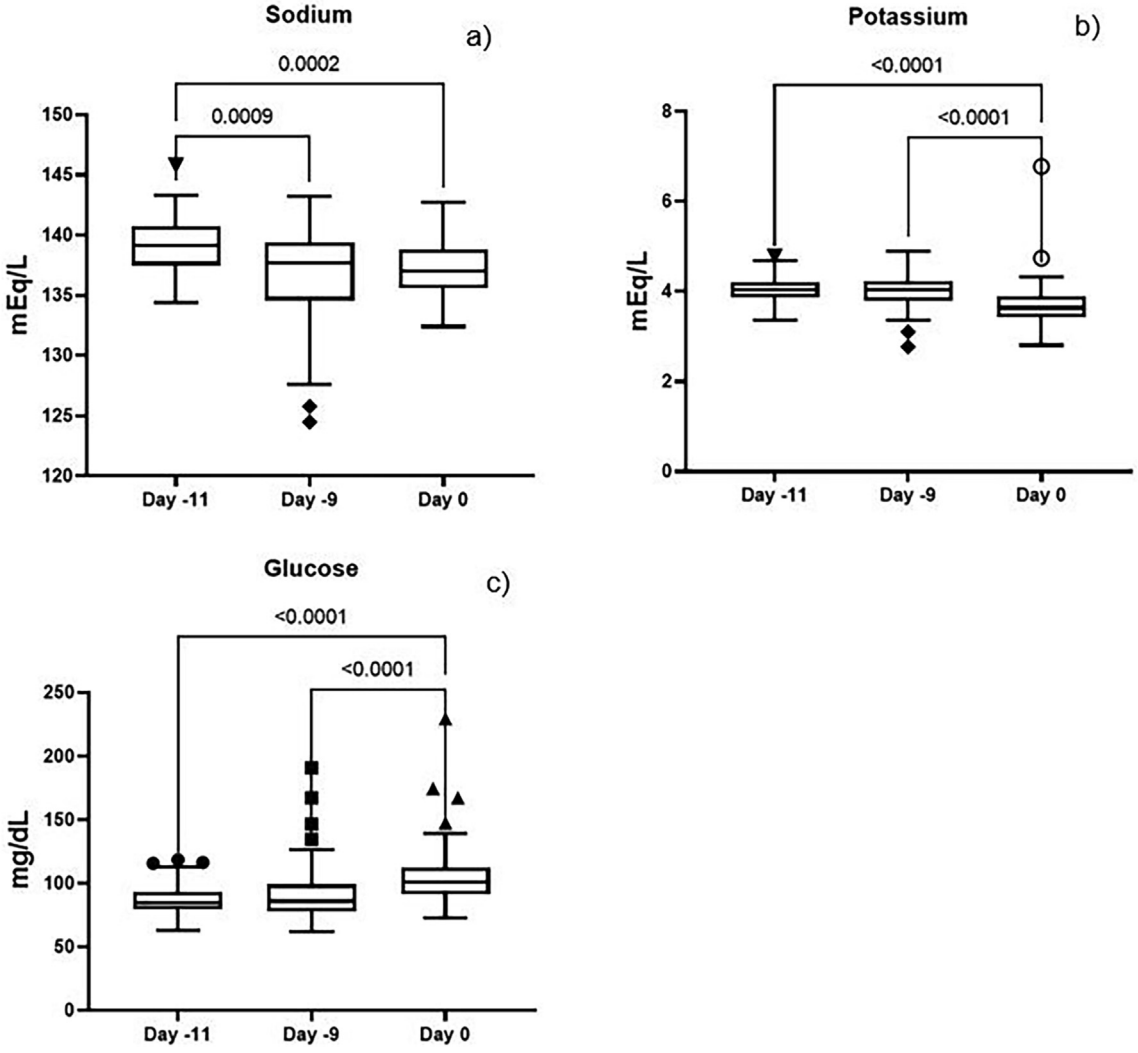


Fig. 2. Serum a) sodium, b) potassium, and c) glucose levels.

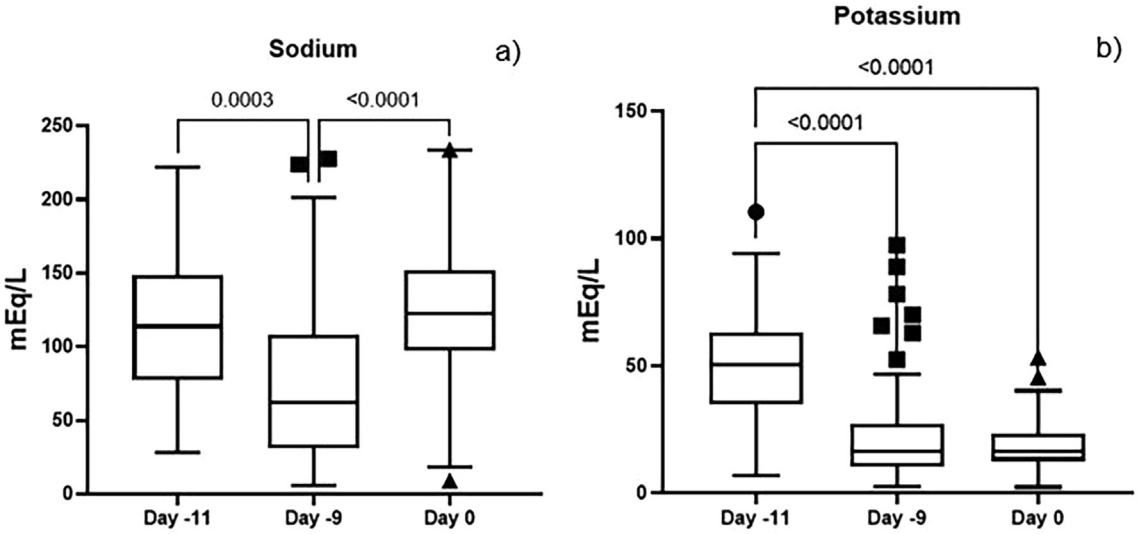


Fig. 3. Estimated glomerular filtration rate by CKD-EPI formula.

immunosuppressor that can deplete leukocytes, including T regulatory cells [16]. Its plasma half-life ranges between 3 and 12 hours, and its metabolites are mainly excreted in urine or bile, depending on the administration route [17,18]. The frequency and intensity of the side effects of Cy are dose-dependent, but also depend on the duration of exposure and each individual's biological susceptibility [19]. Since 2015, we have been doing auto-HSCT in patients with MS employing a modified preparative regimen, now called the "Mexican method" [6]. We have proved that this preparative regimen, which employs the same cumulative doses of Cy used in most immunosuppressive HSCT programs all over the world (200 mg/kg) [20], is endowed with the same immunosuppressive effect but a different toxicity profile to the heart [21], kidney [9], and bone marrow [19]. This diminished toxicity apparently stems from the splitting of the full dose of Cy in two blocks, as seen in Fig. 1. As a result of the installed changes in the preparative regimen, we have had a very low rate of complications and the fatality rate is only 3 in 1300 (0.2%). Along the line of analyzing the toxicity of our modified schedule, we have now engaged in studying the immediate toxicity of our preparative regimen through serum electrolytes and other metabolic changes. The salient finding is hyponatremia, which resulted in the admittance of two patients to the hospital as a result of drug-induced hyponatremia-related seizures. After the first cycle of treatment with Cy (day −9), the incidence of hyponatremia was 27%, and after the second cycle (day 0), it was 10%. The physiopathology originates from self-limited inappropriate antidiuretic hormone secretion mediated by the effect of Cy on the renal tubule, with an increase in water reabsorption and sodium wasting [22], given that Cy induces a short-term upregulation of vasopressin receptor type 2 and aquaporin-2 expression in the kidney [23]. Only 2.1% of our patients developed hyponatremia-mediated complications that warranted hospitalization, in all instances for less than 24 hours. To counteract the hemorrhagic cystitis associated with Cy, aggressive oral hydration is recommended to the patients, leading to a great increase in urinary output in comparison with baseline values and, in turn, an increase in the frequency of hypotonic hyponatremia. By employing water with electrolytes, this dilutional effect can be diminished in the patients.

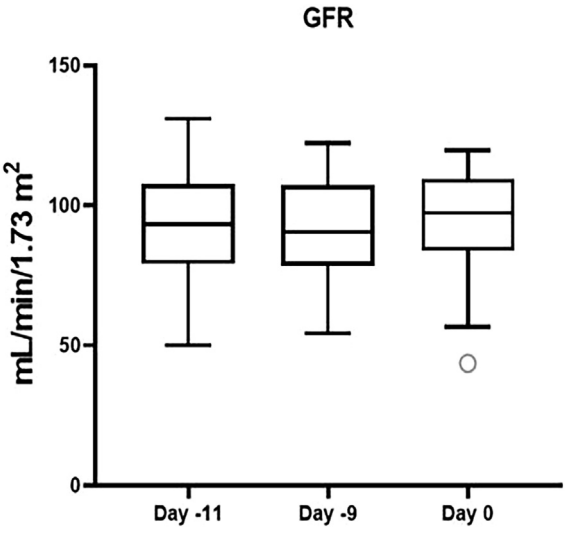


Fig. 4. Urinary a) sodium and b) potassium.

Furthermore, 5 patients presented hyperglycemia on day −9 (median = 146, IQR = 48.4) and 10 patients at day 0 (median = 138, IQR = 34.7). We detected 53% of cases of hyperglycemia on day 0, of which 22.6% exceeded 126 mg/dL. Nonetheless, the affected

Table 2. Summary of electrolyte abnormalities in serum

Serum	Abnormalities	Day −11	Day −9	Day 0
Sodium	Hyponatremia	1 (1.3%)	20 (27%)	12 (16%)
Sodium and osmolarity	Isotonic Hyponatremia	1 (1.3%)	7 (9%)	12 (16%)
	Hypotonic Hyponatremia	0 (0%)	13 (17%)	0 (0%)
Potassium	Hypokalemia	4 (5.3%)	6 (8%)	29 (38.7%)
	Hyperkalemia	0 (0%)	1 (1.3%)	1 (1.3%)
Chloride	Hypochloremia	0 (0%)	5 (6.7%)	1 (1.3%)
	Hyperchloremia	0 (0%)	0 (0%)	1 (1.3%)
Ionized calcium	Hypocalcemia	42 (56%)	68 (90.7%)	71 (94.7%)
	Hypercalcemia	0 (0%)	0 (0%)	0 (0%)
Glucose	Hypoglycemia	3 (4%)	4 (5.3%)	0 (0%)
	Hyperglycemia	0 (0%)	5 (6.7%)	10 (13.3%)
Uric acid	Hyperuricemia	6 (8%)	5 (6.7%)	16 (21.3%)

patients were asymptomatic, and this event can be attributed to the use of dexamethasone on the same days that cyclophosphamide was administered. It appears to result from a potassium and insulin feedback loop, whereby hypokalemia inhibits insulin secretion [24]; Cy may be an additional risk factor for acute hyperglycemia, since high doses of Cy are associated with temporary depletion of immunoregulatory cells, and increased production of interferon alpha and type 1 T-helper [25] that are is capable of directly causing the destruction of islet cells.

Analysis of the glomerular filtration rate yielded no statistically significant differences: Urea and BUN values decreased significantly after the first cyclophosphamide dose but returned to baseline levels after the second dose, this being another proof of the diminished nephrotoxicity of the "Mexican method" [9]. Furthermore, the estimated glomerular filtration rate according to the CKD-EPI formula, and as recommended by the Kidney Disease Improving Global Outcomes (KDIGO) guidelines [26], is not affected by the conditioning and mobilization protocols, thus confirming the regimens' patient safety profile.

Hypokalemia after mobilization and conditioning (day 0) may be a direct consequence of passive transcellular exchange in response to hyperglycemia, promoting the movement of water from the intracellular to the extracellular space [27]. Serum uric acid levels increased significantly but never led to clinical manifestations in patients with values above 6.8 mg/dL.

This study has some limitations. First, the number of patients in the cohort was limited. Additionally, measurement on day −2 before apheresis would reveal the differences between the post-mobilization phase and the post-conditioning phase (day 0). However, the findings of this study provide useful information for future research on HSCT.

In summary, we found changes in the concentration of electrolytes and some metabolites following a conditioning regimen with Cy and filgrastim; the salient changes were significant for both hyponatremia and hyperglycemia. However, these changes do not compromise the transplantation protocol and hospitalizations never lasted longer than 24 hours, and were exceptional cases (2 cases). Cy-induced hyponatremia may be ameliorated by employing oral electrolytes. Our results support the diminished renal toxicity of our conditioning method and indicate tolerable changes in electrolytes; these data add to the previously reported safety of the "Mexican method".

Authorship contribution statement

Brenda J. Méndez-Laureano: Conceptualization, Investigation, Data curation, Writing − original draft. Moisés Manuel Gallardo-Pérez: Conceptualization, Data curation, Methodology, Formal analysis, Writing − review & editing. Claudia Minutti-Zanella: Investigation, Data curation, Writing − original draft. Guillermo J. Ruiz-Argüelles: Supervision, Writing − review & editing, Methodology.

Conflict of interest

All authors declare that they have no conflicts of interest.

Appendix A

Supplementary Table 1. Serum differences between day −11 and day −9.

Group	Median (IQR)	*P*
Urea	29.2 (9.3) vs 25.4 (7.2)	<0.001
BUN	13.6 (4.44) vs 11.85 (3.36)	<0.001
Uric acid	4.91 (1.58) vs 4.745 (1.41)	0.188
Ionized calcium	4.03 (0.26) vs 4.12 (0.34)	0.05
Sodium mEq	139.1 (3.19) vs 137.7 (5.2)	0.001
Chloride mEq	105.45 (3.7) vs 103.4 (6)	0.003

Supplementary Table 2. Serum differences between day −11 and day 0.

Group	Median (IQR)	*P*
Glucose	84.8 (14.1) vs 100.8 (20.4)	<0.001
BUN	13.6 (4.44) vs 13.18 (4.05)	0.962
Uric acid	4.91 (1.58) vs 5.82 (1.63)	<0.001
Ionized calcium	4.03 (0.26) vs 3.98 (0.34)	0.291
Sodium mEq	139.1 (3.19) vs 137 (3.2)	<0.001
Potassium mEq	4.03 (0.35) vs 3.635 (0.48)	<0.001

Supplementary Table 3. Serum differences between day −9 and day 0.

Group	Median (IQR)	*P*
Glucose	86 (22.6) vs 100.8 (20.4)	<0.001
Urea	25.4 (7.2) vs 28.3 (8.7)	0.002
BUN	11.85 (3.36) vs 13.18 (4.05)	0.009
Uric acid	4.745 (1.41) vs 5.82 (1.63)	<0.001
Ionized calcium	4.14 (0.34) vs 3.98 (0.34)	0.001
Potassium mEq	4.03 (0.47) vs 3.635 (0.48)	<0.001
Chloride mEq	103.4 (6) vs 105.4 (3.69)	0.001

Supplementary Table 4. Urine differences between day −11 and day −9.

Group	Median (IQR)	*P*
Urinary output	40 (30) vs 62.5 (40)	<0.001
Sodium	111.2 (65.8) vs 65.3 (76.1)	<0.001
Potassium	49.985 (29.71) vs 16.81 (16.17)	<0.001
Chloride	106.2 (74.4) vs 69.85 (69.15)	<0.001

Supplementary Table 5. Urine differences between day −11 and day 0.

Group	Median (IQR)	*P*
Urinary output	40 (30) vs 70 (37.5)	<0.001
Potassium	49.985 (29.71) vs 16.355 (10.94)	<0.001

Supplementary Table 6. Urine differences between day −9 and day 0.

Group	Median (IQR)	*P*
Urinary output	62.5 (40) vs 70 (37.5)	0.471
Sodium	65.3 (76.1) vs 121.7 (61.8)	<0.001
Potassium	16.81 (16.17) vs 16.355 (10.94)	0.931
Chloride	69.85 (69.15) vs 101.7 (55.85)	0.002

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