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Correspondence

The effect of post-transplant spironolactone on daily potassium requirements in patients undergoing autologous stem cell transplantation

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Excessive potassium (K^+) loss is frequently seen post-transplant following platinum containing high-dose chemotherapy (HDC) regimens such as STAMP-I (cyclophosphamide + carmustine + cisplatin), STAMP-V (cyclophosphamide + thiotepa + carboplatin), ICE (ifosfamide + carboplatin + etoposide) and TMCb (thiotepa + melphalan + carboplatin).[1–3] Nephrotoxic antibiotics which are commonly used in the post-transplant period may also cause hypokalemia. In general, the etiology of post-transplant hypokalemia is multi-factorial. Manifestations of hypokalemia seldom occur unless the plasma K^+ is $<<$ 3 mEq/l. Profound K^+ depletion is associated with an increased risk of cardiac arrhythmias and also rhabdomyolysis. Smooth-muscle function might also be affected and might manifest as paralytic ileus.[4] The main reasons for profound hypokalemia after HDC are renal and gastrointestinal K^+ loss due to nephrotoxicity from platinum or antibiotics and diarrhea associated with gastro-intestinal (GI) mucositis, due to alkylating agents such as thiotepa, melphalan and cyclophosphamide. Therefore, close follow-up of K^+ levels is crucial for the first 2–3 weeks after transplantation. Daily K^+ requirements in this setting may reach as much as 150–200 mEq/l/day. Whole day K^+ replacement can be a time-consuming process and must be carried out with care. We therefore attempted to investigate the effect of spironolactone (100 mg tablet, twice daily), which is a potent aldosterone antagonist, on K^+ loss following HDC. We hypothesized that administration of spironolacone during the post-transplant period may counterbalance the renal K^+ loss by antagonizing aldosterone, thus decreasing K^+ requirements.

Between 1999 and 2001, 40 consecutive patients meeting the eligibility criteria, with hematologic malignancies and solid tumors, were entered into a study evaluating the effect of spironolactone on daily potassium requirements following the TMCb conditioning regimen which causes excessive potassium loss. Patient characteristics are listed in Table 1. Oral and written informed consent for PBSC collection and transplantation was obtained from all patients or their guardians. All patients received thiotepa 250 mg/m^2/day (on days -9 and -8), melphalan 50 mg/m^2/day (on days -7 and -6) and carboplatin 400 mg/m^2/day (on days -5, -4 and -3) (TMCb regimen).[3] Patients rested on days -2 and -1 and PBSCs were infused on day 0.

Two sequential groups of patients participated this study. The first 20 patients did not receive spironolactone and the second 20 patients received spironolactone 100 mg tablet twice daily per orum starting on day 0 and continuing up to post-transplant day +15. Because of the close association of hypokalemia with hypomagnesemia, daily serum K^+ and magnesium (Mg) levels were followed.[5] We attempted to keep serum K^+ and Mg^{++} levels $\geqslant$3.5 mEq/l and $\geqslant$1.5 mEq/l in every patient, respectively. Median total K^+ requirements over 15 days in patients receiving and not receiving spironolactone were 710 mEq (range 160–2250)

Table 1 Patient characteristics ($n = 40$)

Variable	*Spironolactone (n = 20)*	*Without spironolactone (n = 20)*	*P value*
Sex (Male/Female)	9/11	10/10	0.75
Age (years) (median range)	31 (17–57)	30 (16–62)	0.94
Weight (kg) (median range)	65.5 (47–105)	64.5 (45–99)	0.89
PBSC mobilization regimens	17		0.53
CY + etoposide + rhG-CSF	3	15	
CY + epirubicine + rhG-CSF	0	4	
CY + taxol + rhG-CSF		1	
Diseases			
Lymphoma	11	10	0.55
Breast cancer	5	4	
Testicular cancer	2	3	
Other	2	3	
No. of prior cycles of chemotherapy median (range)	6 (3–16)	6.5 (4–14)	0.71
Time from mobilization to transplant (days) (median range)	33.5 (28–40)	34.5 (27–46)	0.81
Number of infused $CD34^+$ cells $\times 10^6$/kg (median range)	4.49 (2.40–11.46)	4.64 (2.68–10.44)	0.98
Conditioning regimen (TMCb)	20/20	20/20	
TPN requirement (days) (median range)	4 (0–12)	4 (0–11)	0.92
No. of days of aminoglycoside (median, range)	4 (0–7)	4 (0–6)	0.96
No. of days of antifungal treatment	2 (0–5)	3 (0–5)	0.62

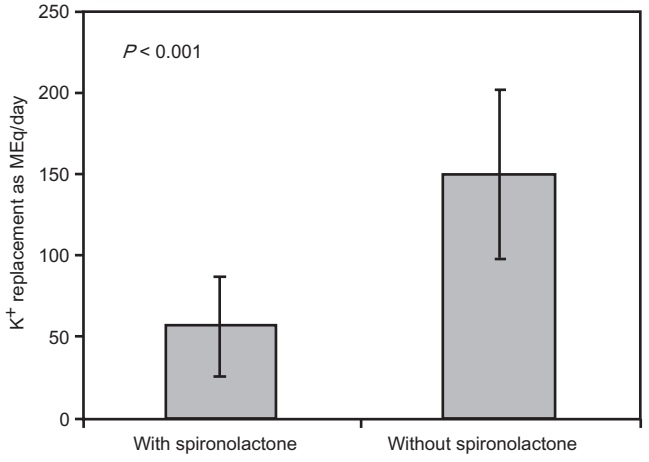


Figure 1 Daily K^+ requirements in patients receiving and not receiving spironolactone administration.

and 2185 (1430–4830), respectively. The median of the mean daily K^+ requirements in patients on and off spironolactone were 47.33 mEq (range 10.67–150) and 145.67 (95.33–322), respectively ($P < 0.001$) (Figure 1). As a result, post-transplant spironolactone administration significantly decreased renal K^+ loss and daily K^+ requirements in patients receiving a platinum-containing conditioning regimen. In addition, none of the patients in this study had hyperkalemia as a result of spironolactone administration.

Although the etiology of post-transplant hypokalemia is multifactorial, renal K^+ loss which is mainly due to platinum-containing HDC regimens plays an important role. Platinum compounds are commonly used chemotherapeutic agents which are associated with significant acute and chronic renal toxicity. These compounds may induce renal function damage identical to that found in primary renotubular hypomagnesemia-hypokalemia with hypocalciuria.[6] Therefore, hypokalemia and hypomagnesemia due to renal Mg^{++} and K^+ losses are common electrolyte abnormalities in patients receiving platinum containing HDC regimens. Close follow-up of K^+ and Mg^{++} levels in the post-transplant period is thus important. It is well known that there is a close association between refractory K^+ depletion and Mg deficiency.[5] Thus, as in the current study, both serum K^+ ion and Mg^{++} levels should routinely be assessed in patients who receive a platinum-containing HDC regimen.

Renal excretion is the major route of elimination of excess K^+. Ninety percent of filtered K^+ is reabsorbed by the proximal convoluted tubule and loop of Henle. Net distal K^+ secretion or reabsorption occurs in the setting of K^+ excess or depletion, respectively. K^+ secretion is regulated by two physiologic stimuli: aldosterone and hyperkalemia. Aldosterone is secreted in response to high renin and angiotensin II or hyperkalemia. Spironolactone, a potent aldosterone antagonist, acting on the distal half of the convoluted tubule and the cortical portion of the collecting duct by competitive inhibition of aldosterone, thereby blocking the exchange between sodium and both K^+ and hydrogen in the distal tubules and collecting ducts. Therefore, this agent produces a sodium diuresis and K^+ retention.[7] In the current study, we attempted to exploit this effect of spironolactone in order to prevent renal K^+ loss in patients receiving platinum-containing HDC regimen. As a result, post-transplant spironolactone administration significantly decreased renal K^+ loss and daily K^+ requirements in patients receiving platinum containing conditioning regimens.

K^+ can only be replaced at a rate of about 15–20 mEq/h by infusion. Clinicians may therefore overcome this problem by decreasing daily K^+ requirements with the post-transplant administration of spironolactone, which may be time saving and cost-effective.

T Demirer[1,2]
M Aylı[1]
M Daglı[3]
T Fen[3]
R Haznedar[4]
N Ustael[1]
T Ustun[1]
A Oymak[1]
O Ozdel[1]
O Muftuoglu[1]

[1]*Ankara Numune Education and Research Hospital, Bone Marrow Transplantation Unit, Ankara, Turkey;* [2]*Ankara University Medical School, Dept of Hematology/Oncology, Ankara, Turkey;* [3]*Ankara Oncology Hospital, Ankara, Turkey; and* [4]*Gazi University Medical School, Dept of Hematology and Medical Oncology, Gazi, Turkey*

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