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CLINICAL STUDY

Potassium Binders in Hemodialysis Patients: A Friend or Foe?

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Abstract

There is insufficient evidence on the utility of potassium-binding resins in patients with end-stage renal disease on dialysis. In addition, their poor tolerability raises concerns of patient adherence. We aimed to assess the efficacy of calcium resonium and investigate the impact of counseling on adherence pattern as well as treatment response. Adult patients on hemodialysis receiving calcium resonium were enrolled with a control group not on treatment. Adherence patterns and adverse effects were recorded following patient interviews. Patients were stratified into 28 adherent (A), 42 non-adherent (NA), and 30 controls (C). Patient education was undertaken, and serum potassium levels were evaluated for 3 months pre- and post-counseling with inter- and intra-group comparison. A statistically significant difference was observed between potassium levels at baseline in A and NA groups but not post-education, which was related to worsening control in former and not due to improvement in NA patients. The poor effectiveness of calcium resonium in the control of hyperkalemia was likely related to non-compliance due to gastrointestinal (GI) intolerability. Dietary indiscretions as well as lack of consistent use of cathartics may have also contributed. No difference in dialysis adequacy was noted among groups, although the contribution of residual renal function was not assessed. These findings raise concern regarding cost-efficacy of this medication and lend credence to investing in traditional measures in hyperkalemia management, namely dietary compliance and adequate dialysis. Further long-term trials are awaited to better define the role of calcium resonium in the dialysis setting.

Keywords: potassium binders, resins, calcium resonium, hemodialysis, compliance

INTRODUCTION

Potassium-binding resins have been on the market long before the US FDA, and other healthcare authorities required stringent evidence to demonstrate drug safety and efficacy prior to marketing approval. Sodium polystyrene sulfonate (*Kayexalate*) was approved in 1958 by the US FDA, as a potassium-binding resin in the colon, for the management of hyperkalemia.[1] Similarly, calcium resonium or calcium polystyrene sulfonate has been approved for use in Europe. The use of potassium-binding resins has proven to be of value in the pre-dialysis chronic kidney disease (CKD) setting and in the management of emergency hyperkalemia; however, there is insufficient evidence regarding its efficacy and utility in patients with end-stage renal disease on dialysis.[2,3] Moreover, the poor tolerability of these agents raises concerns of patient adherence to this relatively costly treatment. In addition, previous studies have documented bowel necrosis primarily in post-operative, dialysis, and transplant patients receiving sodium polystyrene sulfonate with sorbitol.[4] In our 250-patient hemodialysis unit, the use of calcium resonium in patients with elevated pre-dialysis potassium levels (>6 mmol/L) is a common practice. Our objective is to assess the efficacy and tolerability of calcium resonium retrospectively and to prospectively investigate the impact of patient education on their adherence pattern as well as their response to treatment.

METHODS

All adult patients on hemodialysis receiving calcium resonium were enrolled in this retrospective study ($n = 70$); a group of randomly selected hemodialysis patients ($n = 30$) not receiving calcium resonium served as the control group. Serum potassium levels were

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Table 1. Patient demographics and hemodialysis parameters.

	Adherent group	Non-adherent group	Control group
Demographics	$N = 28$	$N = 42$	$N = 30$
Age (years)	54.5 ± 17.9	61.8 ± 16.8	48.9 ± 18.7*
Sex	F (61%) M (39%)	F (55%) M (45%)	F (48%) M (52%)
Diabetes	46%	57.5%	47%
Dialysis parameters			
Duration of hemodialysis (months)	88.5 ± 81.7	62.3 ± 47	35.6 ± 33.4*
Modality of dialysis	HD (36%) HDF (64%)	HD (41%) HDF (59%)	HD (41%) HDF (59%)
Access type	Catheter (21.4%)	Catheter (31%)	Catheter (40%)
Access flow (mL/min)	1319.4 ± 934	1268 ± 857	1583.3 ± 973.5**
Kt/V	1.3 ± 0.3	1.2 ± 0.2	1.3 ± 0.2**
Blood flow (mL/min)	330 ± 36	312.3 ± 47.1	351.5 ± 233.2**
Laboratory parameters			
Hb (g/L)	11.2 ± 1.2	11.4 ± 1.6	11.9 ± 2**
Alb (g/dL)	36 ± 3.2	33.9 ± 3.4	36.7 ± 2.8**
Medications			
Patients on insulin	12	20	9
Patients on ACEI/ARB	6	9	3
Patients on furosemide	1	0	0
Patients on lactulose	7	19	NA

Notes: HD, hemodialysis; HDF, hemodiafiltration.
p-Value versus controls (ANOVA): * $p < 0.05$, ** p = NS.

retrospectively retrieved from the Health Information System for a period of 3 months; adherence patterns and adverse effects to treatment were recorded following patient interviews. Patients were accordingly stratified into three groups: a group of 28 adherent patients (A), a group of 42 non-adherent patients (NA), and a control group (C). Patient demographics and dialysis parameters are described in Table 1. A patient educational intervention followed to emphasize the importance of adherence to their calcium resonium regimen, and subsequently, serum potassium levels were prospectively monitored for a 3-month period. Baseline potassium levels were calculated using values for the first 3 months of treatment prior to the educational interventions; similarly, post-education potassium levels were the three monthly averages following patient counseling. Inter-group results were analyzed using analysis of variance (ANOVA) statistical test. Intra-group results before and after the educational intervention were compared using paired Student *t*-test. Approval from the hospital's Research Ethics Committee was obtained.

RESULTS

Patient demographics (Table 1) show equivalent male–female distribution and proportion of diabetic patients. The controls were younger than the treatment groups. There was equivalent percentage on hemodiafiltration (HDF) versus conventional hemodialysis and dialysis adequacy reflected by *Kt/V* was also similar inspite the controls having a higher percentage with PermCath as their dialysis access. Access flow and achieved blood flow were not different between groups and all patients in the treatment group except one had a dialysate potassium bath of 2 meq/L. Hemoglobin level and nutritional status as reflected by serum albumin were also similar between groups. No hyperkalemia-related mortality was observed, and none of the study patients required extra or urgent dialysis sessions for hyperkalemia.

Comparing intra-group variability before and after the educational intervention, our results shown in Table 2 indicate that there were no statistically significant differences in potassium levels in both patient groups following intensive sessions of education. Serum potassium values increased from 5.17 ± 0.42 mmol/L to 5.42 ± 0.74 mmol/L after education ($p = 0.06$) in the adherent group and decreased from 5.56 ± 0.58 mmol/L to 5.48 ± 0.65 mmol/L ($p = 0.4$) in the non-adherent patient group. These results may potentially be translated into a slight improvement in adherence to calcium resonium treatment in the non-adherent group coupled with a larger regression in adherence in the initially adherent group, both cases being statistically insignificant. Intolerance to treatment was related to gastrointestinal (GI) adverse effects, namely nausea and vomiting in 98% of the non-adherent group. Inter-group variability as assessed using ANOVA statistical test indicated a significant difference in baseline potassium levels (A = 5.17 ± 0.42, NA = 5.56 ± 0.58, C = 5.08 ± 0.69; $p = 0.0015$) and potassium levels post-education (A = 5.42 ± 0.74, NA = 5.48 ± 0.65, C = 4.88 ± 0.58; $p = 0.0006$), a difference mostly attributed to the fact that patients in the control group had generally lower potassium levels not necessitating treatment with calcium resonium. Of note, the controls did not undergo the intensified education intervention beyond the usual nutritional counseling, and their serum potassium level was measured initially and at study end. Moreover, a statistically significant difference was observed between potassium levels at baseline in the adherent and

Table 2. Potassium levels before and after education intervention with intra- and inter-group comparisons.

	Adherent group	Non-adherent group		Inter-group p-value
Potassium level before education (mmol/L)	5.17 ± 0.42	5.56 ± 0.58		$^{*}p = 0.003$
Potassium level after education (mmol/L)	5.42 ± 0.74	5.48 ± 0.65		$^{*}p = 0.71$
	Adherent group	Non-adherent group	Control group	
Potassium level before education (mmol/L)	5.17 ± 0.42	5.56 ± 0.58	5.08 ± 0.69	$^{**}p = 0.0015$
Potassium level after education (mmol/L)	5.42 ± 0.74	5.48 ± 0.65	4.88 ± 0.58	$^{**}p < 0.001$
Intra-group p-value	$^{***}p = 0.06$	$^{***}p = 0.4$	***NA	

Notes: $^{*}p$-Value A versus NA.
$^{**}p$-Value versus controls.
$^{***}p$-Value before and after education.

non-adherent groups ($p = 0.003$) but not post-education ($p = 0.71$) as shown in Table 2. This was mainly related to a worsening in potassium levels in the adherent group and not to an improvement in the non-adherent group.

DISCUSSION

Hyperkalemia is common in patients with end-stage renal disease and may result in serious cardiac conduction abnormalities. Dialysis is the cornerstone of treatment of hyperkalemia in these patients. Prevention of hyperkalemia currently rests largely upon dietary compliance and avoidance of medications that may promote hyperkalemia.[5] Calcium resonium is a cation exchange resin prepared in the calcium phase. Each gram of resin has a theoretical in vitro exchange capacity of about 1.3–2 mmol of potassium. In vivo, the actual amount of potassium bound will be less than this. The drug is given as 15 g once to 4 times daily as slurry in water or syrup. Calcium resonium acts by a cumulative process throughout the GI tract. Potassium is taken up in increasing amounts in exchange for calcium ions, removing potassium ions which are carried away in the feces. Importantly, however, calcium resonium is not absorbed from the GI tract.[6] Moreover, the efficiency of potassium exchange is unpredictably variable, and the resin is not selective for potassium.

There is insufficient evidence to demonstrate a definitive role for potassium-binding resins in the preventive management of hyperkalemia in the dialysis setting. Our results suggest suboptimal patient adherence to treatment with calcium resonium due to GI intolerability, namely nausea and vomiting. The adherence of patients was not sustained, even in those who were labeled as adherent; meanwhile, a relationship between the educational intervention and response to treatment could not be demonstrated. Factors that may generally contribute to the development of hyperkalemia and worsen its treatment response include the dietary habits, medications, and suboptimal dialysis adequacy. Compliance with dietary recommendations presents as the ultimate challenge in managing hyperkalemia in our patient population. Patients in the United Arab Emirates tend to consume large amounts of dates, coffee, and tea that have high dietary potassium content. Additionally, medications such as angiotensin-converting-enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) may be additional contributing factors. The NA group was noted to have more patients on ACEIs/ARBs; however, their hyperkalemic effects may be negligible in the setting of end-stage renal disease. In addition this group also included more diabetic patients on insulin which tends to reduce potassium levels. Accordingly, inter-group variability in medication regimens was not expected to affect our interpretation of treatment outcomes.

As importantly, it is established that co-prescribing calcium resonium with a cathartic such as lactulose serves to enhance the elimination of bound potassium and relieves possible constipation. However, standardizing such practice remains controversial particularly following the US FDA release in 2009 that has warned against the use of Kayexalate-sorbitol combination. Cases of colonic necrosis and other serious GI adverse events (bleeding, ischemic colitis, and perforation) have been associated with this cathartic-potassium-binding resin combination.[7] Moreover, there has been no convincing evidence that adding sorbitol to the resin increases its effectiveness in the treatment for hyperkalemia. Nevertheless, to our knowledge, lactulose has not been associated with similar adverse events observed with sorbitol. Only 37% of patients in the A (25%) and NA (45%) groups combined were receiving lactulose concomitantly. It is plausible that co-prescribing lactulose with calcium resonium might have improved response to treatment.

Finally, we also analyzed the parameters that impact the adequacy of dialysis in our patient groups as shown in Table 1. No statistically significant difference was observed in terms of the effects on serum potassium levels of dialysis modality, access flow, blood flow, and Kt/V keeping in mind that potassium content in dialysate solution was not different between groups. However, a significant inter-group difference in the duration on dialysis was observed between the control group and the other two groups with the control group having the shortest duration ($p < 0.05$). Despite this and while having the highest number of patients with catheter access type (40%), they still maintained the lowest serum potassium levels. Nevertheless, this group had the highest dialysis

access and blood flow perhaps contributing to this, yet their dialysis adequacy was not statistically different.

CONCLUSION

Calcium resonium has poor effectiveness in the control of hyperkalemia in our dialysis patients. This is mostly related to GI intolerability explaining patient non-adherence. The main additional factor which has been highlighted, as likely contributing to its partial efficacy, is the poor compliance with dietary potassium restriction. Nevertheless, we were unable to demonstrate any differences related to dialysis adequacy. Surprisingly, no benefit was observed, from this short-term study, between extensive patient education and response to treatment.

These findings raise concerns of cost-efficacy with this relatively expensive medication. While life-threatening hyperkalemia should be prevented at any cost, options exist to limit the use of calcium resonium to only those patients who can tolerate it and prescribing it on an "as needed" basis in relation to dietary potassium intake. This will serve as an attempt to optimize the use of this agent in the dialysis setting and avoid unnecessary cost burden. Finally, investing in traditional factors in the management of hyperkalemia, dietary compliance, and adequacy of dialysis remains the mainstay of treatment. This study sets the ground for further long-term trials designed to establish robust evidence and better define the role of calcium resonium in the dialysis setting.

***Declaration of interest*:** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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