Research Article

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Management of mild hyperkalemia with sodium polystyrene sulfonate: is it necessary?

Aim: There is no consensus defining clinically significant hyperkalemia or settings which require potassium (K^+) lowering therapy. We explored the management of mild hyperkalemia, defined as a serum K⁺ ≤5.6 mEq/l, when treated with sodium polystyrene sulfonate (SPS). Materials & methods: Medical records of patients ≥18 years, who had received SPS for serum K⁺ ≤5.6 mEq/l, were reviewed. Results: A total of 106 SPS doses were given to 92 patients for a serum $K^+ \leq 5.6$ mEq/l. Significant delays between the pre-SPS serum K⁺ and SPS administration and between SPS administration and followup serum K⁺ were evident. Conclusion: Mild elevations in potassium, which may not be clinically significant, are often treated with SPS while its therapeutic monitoring remains inadequate.

Keywords: cation-exchange resin • ECG • hyperkalemia • management • mild • potassium sodium polystyrene sulfonate

Hyperkalemia is a common metabolic complication affecting 1-10% of hospitalized patients annually in the USA [1-4] with an associated mortality of one in 1000 hospitalized patients [5]. Based on a recent validation study, the reported incidence of hyperkalemia may be underestimated due to the low sensitivity of the ICD-10 code for hyperkalaemia (E87.5), making it an even larger threat than we may realize [6]. Widely used medications such as RAAS blockers, mineralocorticoid receptor antagonists and others including nonsteroidal anti-inflammatory drugs, trimethoprim-sulfamethoxazole and potassium supplements in some part are responsible for 35-75% of hyperkalemia cases [7-9], and their increased use implicates a rising incidence of hyperkalemia [10,11]. Declining renal function is also a major predisposing factor for hyperkalemia, with an incidence rate of 75%. The pathophysiology of this finding is directly related to the fact that approximately 90% of potassium is excreted renally [12,13].

Hyperkalemia is caused by extracellular potassium shift or decreased renal potassium excretion. It can be asymptomatic or

present with nonspecific symptoms such as fatigue, weakness, nausea and vomiting or as the much-feared complications of cardiac arrhthymias and muscle paralysis [14]. The treatment of hyperkalemia can be divided into three therapeutic goals - cardiac myocyte stabilization, shifting of potassium into cells and the elimination of potassium from the body. Cardiac stabilization is achieved through calcium gluconate, which shields the myocytes from the effects of potassium, but does not affect the serum potassium level. Agents that shift potassium into cells are insulin/glucose in combination, β-agonists and sodium bicarbonate. Sodium polystyrene sulfonate (SPS), a cation-exchange resin, diuretic therapy and the definitive treatment for hyperkalemia, hemodialysis, are those therapies that eliminate potassium from the body [14].

Although hyperkalemia is a serious and potentially life-threatening condition, there is no consensus defining clinically significant hyperkalemia, nor the clinical settings, which require potassium-lowering therapy, other than a potassium level of greater than



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6.5 with ECG changes. Therefore, the management of hyperkalemia has been and continues to be largely based on the individual physician's discretion and recommendations vary among physicians and institutions [12,15]. The most common ECG changes associated with hyperkalemia are peaked T waves, PR and QRS interval prolongation, loss of p waves, AV block and in impending cardiac failure, sine waves and asystole [16,17]. The sensitivity of ECG changes in detecting hyperkalemia is low, due to the low percentage of patients who present with them (<50%) and poor interpretation by clinicians [18].

Sodium polystyrene sulfonate, commonly abbreviated as SPS, is available in two formulations - with (SPS®; Carolina Medical Products Co., NC, USA) and without sorbitol (Kayexalate®; sanofi-aventis U.S. LLC, NJ, USA). We would like to emphasize that this study deals exclusively with Kayexalate, which is referred to as SPS for the entirety of the paper. SPS is an ion exchange resin that is believed to increase potassium loss via the gastrointestinal tract and is the most commonly used therapeutic intervention for hyperkalemia SPS was introduced in the market in 1958 under Federal Food, Drug, and Cosmetic Act which, in its time, did not mandate the collection of rigorous scientific evidence of efficacy for drug approval required today [19]. Over half a century later, the US FDA issued a warning against the concomitant administration of SPS and 70% sorbitol due to reports of colonic necrosis and perforation. SPS premixed with 33% sorbitol as well as SPS without sorbitol continues to be widely utilized in the setting of hyperkalemia in spite of the emerging literature which suggests that even sorbitol free SPS predisposes to the risk of colonic necrosis and perforation [20]. SPS can be given either orally or rectally, with rectal doses having a much faster onset of action [21].

Given the lack of definitive guidelines, the recently raised concerns about the safety and efficacy of SPS, and the cost of SPS and other therapies utilized in the treatment of elevated serum potassium levels, the present study was undertaken to analyze the time points of diagnosis of hyperkalemia, pharmacologic intervention with SPS and post-intervention follow-up in the in-patient settings.

Methods

Local Institutional Review Board approval was obtained for this study.

Our inclusion criteria consisted of patients 18 years or older who had a prescription order for SPS for serum potassium concentrations of 5.6 mEq/l or less in the emergency department or as in-patients between 1 June 2010 and 31 August 2010 at New York Hospital Queens were included in the current analysis. Patients requiring emergent dialysis were excluded. A total of 92 patients who had been prescribed SPS between 1 June 2010 and 31 August 2010 were identified via the New York Hospital Queens pharmacy. Electronic medical records were reviewed retrospectively for all identified patients who had been prescribed a dose of SPS between 1 June 2010 and 31 August 2010. Age, gender, BMI (body mass index), as well as serum potassium concentrations before and after SPS administration were tabulated and time intervals were calculated.

Pre-intervention time interval was defined as the interval between the time at which serum potassium result was reported and the subsequent administration of SPS. Post-intervention time interval was defined as the time interval between the administration of SPS and the time at which follow-up serum potassium was drawn. Statistical analysis utilizing paired t-test to compare serum potassium concentration before and after SPS administration was performed using SPSS software version 17.

Results

There were 154 patients who were prescribed a total of 249 doses of SPS between June 2010 and August 2010. Seventeen patients did not receive the prescribed SPS dose due to repeat normokalmia or patient condition being inappropriate for administration of SPS. One hundred and twenty-one of the 249 doses of SPS were given for serum potassium levels ≥ 5.7 mEq/l. Of the remaining 111 doses, five were given to patients with no follow up of serum potassium and were therefore excluded (Figure 1). The remaining 106 doses were prescribed to 92 patients with a mean age of 76 ± 13 years, 50% female, for serum potassium of 5.6 mEq/l or less. Patient population characteristics are described in Table 1. SPS was administered 99-times as a single 30-g dose and seven-times as a 15-g dose. Of the 106 doses included in our review, 103 doses were administered orally, one dose via percutaneous enteral gastrostomy (PEG) tube and two doses were given as enemas (Table 2).

The average pre-intervention time was found to be $454 \pm 353 (24-1646)$ min. The average post-intervention time was $637 \pm 423 (84-2016)$ min (Table 3).

The mean pre-SPS serum potassium concentration was 5.37 \pm 0.26 (4.1–5.6) mEq/l while post-SPS serum potassium concentration was 4.84 \pm 0.66 (2.1–6.4) mEq/l. The difference between pre-SPS and post-SPS serum potassium was statistically significant (p < 0.001). However, a number of patients were treated with co-administration of additional potassium lowering agents including insulin with dextrose and β -2 agonists during the same time interval. Therefore, the specific effect of SPS on potassium levels cannot be ascertained from this analysis.

There were only 31 ECGs available within a period of 6 h prior to initiation of treatment for mild hyperkalemia with SPS. None of the available ECGs consisted of changes consistent with hyperkalemia. Seven patients (7.8%) treated for potassium serum concentrations of 5.6 mEq/l or less required potassium supplementation during the same hospital admission due to subsequent development of hypokalemia.

Discussion

The present retrospective review reveals a striking discordance in the theory and practice of the management of hyperkalemia. Due to the protocol design and retrospective nature of the present study as well as limited number of patients with untreated mild hyperkalemia, it was not possible to form a control group for comparison. Nonetheless, our study found that mild hyperkalemia, defined as a potassium level of less than 5.6 mEq/l is often treated aggressively. This clinical practice may be a reflection of the lack of consensus regarding the definition of 'clinically significant hyperkalemia' and ambiguity surrounding the best approach to the management of hyperkalemia. Although the guidelines on the frequency and duration of monitoring of serum potassium concentrations in hyperkalemic patients have not been addressed, it appears reasonable to recheck serum potassium concentrations at least within a window of 1-6 h following therapeutic intervention in the hospital setting.

The large variation in the severity grading of hyperkalemia based on serum potassium levels in the current literature adds to the confusion over which potassium levels need immediate attention, and which do not. Serum concentrations of potassium have been divided into minimal (<6.5 mEq/l), moderate (6.5-8 mEq/l) and severe (>8 mEq/l) by some [22] while others classify 5.1-5.9 mEq/l, 6.0-6.9 mEq/l and greater than 7 mEq/l as mild, moderate and severe hyperkalemia, respectively [23]. Serum potassium concentrations >6.0 mEq/l have also been described as severe hyperkalemia [24], and yet some define hyperkalemia as serum potassium concentration greater than 5.5 mEq/l [25]. Yet others, such as El-Sherif and Turrito, consider serum concentrations of 5.5-7.5 mEq/l to be mild [26]. The wide variation in the classification of hyperkalemia builds confusion and there is a paucity of data to support strict guidelines for therapeutic indications and strategies in different degrees of hyperkalemia.

Moreover, it is important to note that there is no predictor of an individual's cardiac response or electrocardiographic manifestations to different degrees of hyperkalemia [27]. Although the presence of electrocar-



Figure 1. Flow diagram of inclusion process for sodium polystyrene sulfonate doses.

SPS: Sodium polystyrene sulfonate.

diographic changes constitutes a hyperkalemic emergency, studies show that these changes are not sensitive for diagnosing hyperkalemia [28,29]. The earliest electrocardiographic manifestations of hyperkalemia are usually evident at serum potassium concentrations greater than 5.5 mEq/l but are present in only 22% of patients [30-34]. Even with serum potassium concentrations >6.5 mEq/l, only 50% of patients showed hyperkalemia-associated ECG changes [12]. The literature suggests that serum potassium concentrations of 6.0 mEq/l or greater with electrocardiographic changes or serum potassium concentrations >6.5 mEq/l require acute management [25]. However, there is no scientific evidence of one pharmacological intervention being more effective compared with another for the acute management of hyperkalemia [35]. Elliot et al. recommend nonpharmacological therapeutic strategies such as dietary restrictions and discontinuation of hyperkalemia inducing/precipitating medications at serum potassium concentrations greater than 5.5 mEq/l and pharmacological interventions at serum potassium concentrations of 6.0 mEq/l or more [35]. However, the therapeutic indications and strategies for serum potassium concentrations less than 6.0 mEq/l remain ambiguous. Gardner recommended reducing serum potassium concentrations below 6.0 mEq/l as the therapeutic goal in hyperkalemic states [36]. This suggests that serum potassium concentrations below 6.0 mEq/l

Table 1. Demographics.	
Characteristics of patients receiving SPS with serum K ⁺ \leq 5.6 mEq/l	Data
Total number of patients	92
Gender distribution	45 males; 47 females
Age (years)	76.0 ± 13.3
BMI (kg/m²)	27.5 ± 8.0
SPS: Sodium polystyrene sulfonate.	

Table 2. Sodium polystyrene sulfonate dose strengths and routes of administration.		
SPS dosing	Number	
Total number of SPS doses	106	
Dose strength: – 30 g – 15 g	99 7	
Route of SPS administration: – Oral – Rectal – PEG	103 2 1	
PEG: Percutaneous endoscopic gastrostomy; SPS polystyrene sulfonate.	Sodium	

may not require aggressive intervention. Another study recently suggested that even more severe hyperkalemia may not require aggressive therapy or hospitalization [37]. This proposed approach becomes particularly important in view of concerns raised about the efficacy and safety of SPS [20,38-40], the predominant therapy in the management of hyperkalemia [12,40]. Contrarily, a recent retrospective review of 38,689 patients with biomarker-proven AMI, showed increased all-cause mortality in postadmission mean serum potassium levels of \geq 4.5 mEq/l [41]. However, as Perren *et al.* validly point out, the evidence presented by Goyal et al. is weak and limited [42]. More importantly, increased mortality is depicted in the groups of patients with serum potassium \geq 4.5 mEq/l but similar and statistically significant increase is not seen in the incidence of ventricular arrhythmias and cardiac arrests, which would be expected consequent to elevated potassium levels. The all-cause mortality could be influenced by a selection bias of sicker patients which was evident in this cohort since a greater percentage suffered from cardiogenic shock, acute respiratory failure and acute kidney injury in the groups of patients with serum potassium \geq 4.5 mEq/l. In addition, the authors do not describe the hemodynamic status in each group nor do they provide information on other important co-morbidities such as history of malignancy. Interestingly, information on medication use such as calcium gluconate and SPS is lacking. Additionally, whether all patients received the same standard of care is questionable because a lower percentage of patients with serum potassium ≥4.5 mEq/l received cardiac medications

and reperfusion therapies. It is also unclear why the frequency of potassium checks was lower in patients with serum potassium $\geq 5.0 \text{ mEq/l}$ compared with those with serum potassium levels 3.0 to <5.0 mEq/l. Moreover, it is also important to note that the potassium ranges described were a mean of all potassium levels obtained during hospitalization, excluding the first admission potassium level. Although the data were adjusted for multiple confounders, a cause and effect relationship cannot be ascertained from the analysis presented by Goyal *et al.*

Likewise, Einhorn *et al.* reported increased 1-day all-cause mortality in 245,808 patients with 'moderate hyperkalemia' defined as serum potassium \geq 5.5 mEq/l [43]. This also supports the notion that mild hyperkalemia may be not be clinically significant and since the moderate serum potassium threshold was arbitrarily set, it is unknown if a threshold of \geq 5.7 mEq/l would alter the findings.

In any case, because hyperkalemia requires the evaluation of multiple factors [14] an individualized approach to the treatment of hyperkalemia is crucial [44]. Though adverse events related to the failure to treat hyperkalemia are unacceptable, the over-treatment of mild hyperkalemia in stable, asymptomatic patients puts them at risk for iatrogenic harm from potassiumlowering agents such as SPS [45]. Furthermore, the use of SPS in the management of mild and clinically insignificant hyperkalemia becomes highly controversial due to the lack of definitive evidence supporting the efficacy of SPS as a potassium-lowering agent [38,45-46]. To date, no randomized controlled trial has been performed to evaluate the efficacy and safety of SPS, though a recent pediatric study has shown that salbutamol was a safer and more efficacious choice in the treatment of hyperkalemia in comparison to Kayexalate[®] [47]. Fordjour et al. examined the management of hyperkalemia in 154 patients and found SPS to be least effective in the group of patients with mild hyperkalemia defined as serum potassium concentrations of 5.6 mEq/l or less compared with patients with higher potassium concentrations [40]. Notwithstanding, SPS has become an accepted therapy for hyperkalemia and remains the most commonly prescribed medication for hyperkalemia [13,40]. The scope of our findings remains limited due to the small number of ECGs performed prior to SPS dosing but emphasize the discordance in

Table 3. Time intervals between diagnosis, treatment and follow-up.		
Time interval	Mean (min)	Range (min)
From initial serum K ⁺ determination to SPS administration	454 ± 353	24–1646
From SPS administration to F/U serum K+ analysis	637 ± 423	84–2016
SPS: Sodium polystyrene sulfonate.		

considering mild hyperkalemia significant for treatment with SPS without performing ECG and poor monitoring of serum potassium levels. Although, no predictors of an individual's cardiac response to different degrees of hyperkalemia have been established, according to our findings, potassium levels <5.6 mEq/l are unlikely to trigger ECG changes. In addition, the potassium-lowering cocktail (insulin, glucose and calcium gluconate) was prescribed in several cases in our study which makes it difficult to ascertain the role of SPS in mild hyperkalemia. Regardless of the efficacy of SPS as a specific treatment, the findings from this study warrant a clear definition of clinically significant hyperkalemia and guidelines on therapeutic strategies for varying levels of serum potassium, along with parameters for the frequency and duration of monitoring of the serum potassium concentrations after treatment. Based on our findings, we do not recommend the aggressive treatment of mild hyperkalemia (K⁺ \leq 5.6) with SPS. Mild hyperkalemia is often clinically insignificant, and may only need close monitoring and follow-up. We also recommend the confirmation of high potassium levels with a duplicate biochemistry sample prior to initiation of pharmacologic therapy.

In our study, the lag between diagnosis of hyperkalemia and pharmacological intervention had a mean of 454 ± 353 (24–1646) min, while the average time between intervention and follow-up was found to be even longer at 637 ± 423 (84–2016) min. This is especially disconcerting in a condition where the approach to management is often through emergent treatment. In our study sample, there was a long lag between baseline serum potassium concentrations and therapeutic intervention and follow-up serum potassium concentrations, much longer than that has been reported in previous retrospective reviews of hospital management of hyperkalemia [12,40,48]. The retrospective review by Acker et al. also revealed that the time to initial therapeutic intervention was longer in patients with baseline serum potassium concentrations less than 6.5 [12]. This may suggest ambivalence on the part of the evaluators regarding the seriousness of these relatively mild serum potassium elevations. Similar to in-patient management, the follow up of serum potassium concentrations of 6.0 mEq/l or more has been suboptimal in ambulatory settings as well, whereas the average follow-up time has been reported to be 3 days [49,50] and in 10% of outpatient cases, there is no follow-up even after 1 month [49,50]. The implementation of electronic health record systems has not improved the percentage of patients having a follow-up of serum potassium concentrations of 6.0 mEq/l or more within 4 days in the ambulatory setting [49,50]. However, rapid response team interventions specifically designed for hyperkalemia may decrease the time to initiate appropriate therapy according to a retrospective study by Rayan et al. [51].

Conclusion & future perspective

The present retrospective review shows that mild and possibly clinically insignificant hyperkalemia was frequently treated with SPS, with or without additional potassium lowering agents, and that the monitoring of potassium levels before and after therapeutic interventions was inadequate, which may be due to system flaws. These findings serve to stimulate the identification and resolution of system issues as well as education

Practice points

- Hyperkalemia is a potentially serious condition which may require emergent treatment.
- The causes of hyperkalemia are numerous, with etiologies including renal insufficiency and medications such as renin–angiotensin–aldosterone system (RAAS) blockers, angiotensin-converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, trimethoprim-sulfamethoxazole, among others.
- There are no uniform guidelines regarding the classification and treatment of varying degrees of severity of hyperkalemia. The stratification of hyperkalemia is based on physician judgment and institutional guidelines.
- The goals of treatment of hyperkalemia include protection of cardiac myocytes, increasing potassium uptake into cells and elimination of potassium from the body.
- Sodium polystyrene sulfonate or Kayexalate is the most often prescribed treatment for hyperkalemia, although many other therapies are available, including insulin/glucose in combination, β -agonists, sodium bicarbonate and hemodialysis.
- Sodium polystyrene sulfonate has been associated with occasional severe adverse effects including colonic necrosis and perforation.
- Our study showed that mild hyperkalemia is often aggressively treated with sodium polystyrene sulfonate.
- Re-classification of the severity of hyperkalemia, and parameters regarding the treatment of mild, moderate and severe hyperkalemia should be described to reduce iatrogenic harm to patients and to offer uniform and consistent medical care.
- It is also important to confirm high potassium levels with repeat testing before pharmacologic treatment, timely monitor patient response to therapy and follow up patient progression and remove inciting factors for hyperkalemia.

to improve the monitoring of the effect of therapeutic interventions. Therefore, in view of the infrequent but potentially serious adverse events associated with SPS, such as intestinal necrosis and perforation, cost of therapy and possible unnecessary hospitalization or delayed discharge, it may be appropriate to redefine clinically significant hyperkalemia and develop detailed therapeutic guidelines which also emphasize the frequency and duration of monitoring of potassium levels to optimize management of hyperkalemia.

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Ethical conduct of research

The authors state that they have obtained appropriate insti-tutional review board approval or have followed the princi-ples outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investi-gations involving human subjects, informed consent has been obtained from the participants involved.

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