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Original Research Article

Effect of sodium zirconium cyclosilicate in combination with insulin and glucose infusion on hyperkalemia treatment

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Abstract

Purpose: *To evaluate the efficacy of sodium zirconium cyclosilicate (SZC) in combination with insulin and glucose infusion in managing hyperkalemia.*
Methods: *A total of 126 patients, who were admitted with hyperkalemia (≥ 5 mmol/L) to the Yongchuan District Hospital of Traditional Chinese Medicine, Chongqing, China from January 2021 to December 2022, were retrospectively studied. Participants were divided into three groups based on different potassium-lowering regimens, viz, SZC group (40 patients), insulin with glucose (IG) group (38 patients) and SZC + IG group (48 patients). Changes in potassium levels, other serum electrolytes (magnesium, sodium, phosphate, calcium), alanine aminotransferase (ALT) and albumin before and after treatment were recorded. Adverse reactions during treatment were also recorded.*
Results: *Post-treatment, the potassium levels in all three groups exhibited a significant reduction when compared to pre-treatment values ($p < 0.05$). The SZC + IG group showed the highest efficacy, with a significant reduction in blood potassium levels observed 4 h after administration, which was more pronounced compared to other groups. The SZC + IG group, maintained potassium ion concentration at a normal level for a longer duration and no serious adverse reactions were observed during treatment.*
Conclusion: *Intervention with SZC + IG lowers blood potassium levels, maintains it within normal range, and is more effective than the individual use of SZC or IG. A combination of sodium zirconium cyclosilicate, insulin and glucose infusion for treating hyperkalemia will need to be investigated further in a large-scale multicenter study.*

Keywords: *Hyperkalemia, Insulin and glucose infusion, Serum potassium, Sodium zirconium cyclosilicate*

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INTRODUCTION

Hyperkalemia is a metabolic disorder that poses a potential threat to life, as it induces cardiac arrhythmias and elevates the likelihood of mortality [1]. Among individuals with chronic kidney disease and heart failure, hyperkalemia ranks as the most prevalent condition [2,3]. It is known that renin-angiotensin-aldosterone system inhibitors (RAASIs), angiotensin-converting

enzyme inhibitors (ACEIs), aldosterone antagonists (AAs) and angiotensin II receptor blockers (ARBs) increase the risk of hyperkalemia [4-7]. Adjusting or discontinuing RAASI treatment is essential to mitigate recurrent hyperkalemia, as continued use negatively impacts patient prognosis [8-9]. In the last decades, the treatment options for hyperkalemia have been very limited and the current treatment methods are insufficient to meet clinical needs. Sodium zirconium cyclosilicate (SZC) stands as the groundbreaking potassium binder and the first to gain listing in China [10-11]. It accurately captures potassium ions and effectively controls blood potassium levels rapidly and persistently with good overall tolerability [12]. It meets the treatment needs for both acute and chronic management of hyperkalemia, providing an innovative solution for treating hyperkalemia [13]. The effects of Patiromer and SZC in treating hyperkalemia was reported in a systematic review [14]. The findings indicated that SZC significantly lowered serum potassium levels to 0.67 mEq/L after 48 h of administration. The administration of SZC has also been reported to result in a significant decrease in serum potassium levels within 48 h and enabling sustained control of potassium levels within the normal range [15]. Insulin and glucose (IG) infusion is currently an effective intervention in managing acute hyperkalemia. It helps to shift potassium ions from plasma and extracellular space into cells, correcting hyperkalemia [16]. Insulin and glucose infusion demonstrates a fast onset of action, with noticeable reductions in serum potassium levels observed within 15 min of administration [17]. Nevertheless, for individuals undergoing dialysis for end-stage renal failure, this treatment may not be the most advantageous option. Patients with end-stage renal failure achieve potassium clearance through intra-dialytic blood clearances. Sodium zirconium cyclosilicate, insulin, and glucose in combination showed incremental benefits over insulin and glucose alone in the emergency treatment of hyperkalemia, as reported in a double-blind, placebo-controlled Phase II study [18]. Therefore, the objective of this research is to further evaluate the efficacy of SZC + IG in the management of hyperkalemia and generate valuable insights for future treatment strategies.

METHODS

General data

In a retrospective analysis spanning from January 2021 to December 2022, 126 patients who sought medical care at Yongchuan District Hospital of Traditional Chinese Medicine in Chongqing City, China were included. These patients had venous blood potassium levels that surpassed 5.5 mmol/L, indicating high potassium levels. This study has been approved by the Ethics Committee of the First Affiliated Hospital of the Third Military Medical University of Chinese PLA (approval no. Lun Shen 2023 Yan no. 0384). The study protocol followed the principles of the Helsinki Declaration [19] and informed consent was obtained from all patients.

Inclusion criteria

Patients who met the following criteria were included in the study: Individuals that were ≥18 years with high potassium levels (≥ 5.5 mmol/L) and corresponding clinical symptoms of hyperkalemia. Patients were aware of their condition, consented to participate in the study and had complete clinical data.

Exclusion criteria

Patients were excluded from the study if there were data collection errors, or they had taken medications specifically targeting potassium reduction within 24 h before being assessment for the study, or they received repeated doses of treatment. Patients that were already enrolled in other ongoing clinical studies or had food or medications that could impact blood potassium levels were also excluded from the study.

Patient handling and treatment

Basic information such as age, gender, past medical history, major complications, etc., were recorded for all participants. Comprehensive physical examinations including vascular access function, dialysis frequency, blood glucose levels, electrocardiography and medication information related to mineralocorticoid receptor antagonists (MRAs), angiotensin II receptor blockers (ARBs) or renin-angiotensin-aldosterone system inhibitors (RAASIs) were recorded. Based on disease progression and clinical judgment, patients were treated with sodium zirconium cyclosilicate (SZC, 10 g) orally, insulin with glucose infusion (IG, insulin 10IU + glucose, 60 g) intravenously, or a combination of SZC and IG. The number of patients receiving each treatment method was counted and analyzed.

Determination of parameters

Potassium levels

Serum potassium concentrations were determined using an automated biochemical

analyzer before and at specific time intervals (1, 2, 3, and 4 h) after treatment. Hyperkalemia severity was categorized using specific thresholds: severe hyperkalemia referred to venous potassium levels ≥ 6.5 mmol/L, moderate hyperkalemia encompassed the range of 6.0 - 6.5 mmol/L and mild hyperkalemia corresponded to a potassium level of ≥ 5.0 mmol/L.

Electrolytes

Serum calcium, magnesium, sodium and phosphate concentrations were determined before and at specific time intervals (1, 2, 3, and 4 h) after treatment.

Blood glucose

Blood glucose levels were monitored during the treatment period through venous blood sampling.

Nutritional indicators

Alanine transaminase (ALT) and albumin were determined before and after treatment.

Univariate analysis

The relationship between patient factors and prognosis of hyperkalemia was analyzed. Univariate analysis was conducted on 10 factors that may impact treatment of hyperkalemia. Continuous variables were subjected to statistical analysis using either Student's *t*-test or corrected *t*-test, while categorical variables were examined using the chi-Square test or Fisher's exact test in this study.

Statistical analysis

Analysis of data was performed using SPSS 24.0 statistical software. Continuous variables, assuming a normal or uniform distribution, were expressed as mean ± standard deviation. Intergroup comparisons were conducted using the independent-sample t-test. Qualitative data were expressed as percentages and the comparison of these data was performed using either the chi-Square test or Fisher's exact test. A significance level of $p < 0.05$ was used to determine statistical significance.

RESULTS

Characteristics of participants

A total of 126 patients were enrolled in the study. SZC group comprised 24 males and 16 females, with an average age of 52.59 ± 15.32 years. In IG group, there were 20 males and 18 females, with an average age of 54.84 ± 13.23 years. The treatment group included 29 males and 19 females, with an average age of 53.39 ± 14.22 years. No statistically significant differences between the two groups were identified in terms of age, gender, complications and concomitant medications ($p > 0.05$). Overall, among the 126 patients, 60.3 % had an estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m^2, 69.8 % were receiving RAAS inhibitors, 50.8 % had diabetes and 50 % had a history of heart failure (Table 1). No significant differences were found in the incidence of combined diseases among the two groups.

Serum potassium concentrations

Prior to treatment, SZC + IG group had the highest blood potassium levels compared to the other groups and there was no significant distinction ($p > 0.001$). Within SZC + IG group, 75 % of patients exhibited blood potassium levels ≥ 6.5 mmol/L.

Table 1: Characteristic of participants {n, (%)}

Parameter	SZC	IG	SZC+IG	*P*-value
Cases number	40	38	48	
Age (years)	52.59±15.32	54.84±13.23	53.39±14.22	0.7888
Gender				0.7298
Male	24 (60)	20 (53)	29 (60)	
Female	16 (40)	18 (47)	19 (40)	
Serum potassium				<0.001
≥6.5 mmol/L	6 (15)	14 (36.8)	36 (75)	
6.0–6.4 mmol/L	14 (35)	13 (34.2)	8 (16.6)	
5.5–5.9 mmol/L	20 (50)	11 (29)	4 (8.3)	
Changes of ECG hyperkalemia (cases/%)	24 (60)	20 (52.6)	35 (72.9)	0.1424
eGFR <60 mL/min/1.73 m^2	23 (57.5)	23 (60.5)	34 (47.9)	0.1530
Receiving RAAS inhibitors	29 (72.5)	27 (71)	33 (68.75)	0.8234
Diabetes	19 (47.5)	20 (52.6)	21 (43.75)	0.6579
Heart failure	22 (55)	21 (55.2)	30 (62.5)	0.4173

An analysis comparing baseline blood potassium levels between SZC + IG and IG groups did not reveal a statistically significant difference. To evaluate the biological activity of SZC, IG, or SZC + IG treatment, blood potassium concentrations after treatment were analyzed. From the results in Figure 1, compared to baseline, all groups showed statistically significant reductions in blood potassium concentrations after the indicated treatment, with SZC + IG treatment showing the most significant effect. The blood potassium level in the treatment group decreased from a baseline of 5.31 (0.58) mmol/L to 5.11 (0.95) mmol/L (95 % CI -0.2 mmol/L (-0.1513 to 0.5513), p = 0.2597). The average blood potassium concentration in IG group decreased from 5.86 mmol/L at baseline to 4.15 mmol/L (95 % CI 1.304 to 2.116, $p < 0.001$). The combination of SZC and IG treatment with adjunct capsules showed the best biological activity, reducing the blood potassium concentration from a baseline of 6.25 mmol/L to 3.82 mmol/L (95 % CI -2.43 mmol/L (95 % CI, 2.271 to 2.589); $p < 0.001$). These results indicate that, although SZC + IG group had a higher proportion of severe hyperkalemia, the combination treatment with SZC and IG had the most effective potassium-lowering effect.

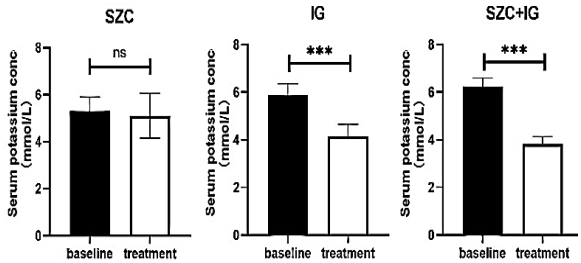

Figure 1: The figure shows the changes in blood potassium concentrations after treatment in the three groups of patients. Mean ± standard deviation is used to report the results. ***$P < 0.001$, and ns signify not significant versus baseline

Urinary potassium excretion

The effect of SZC, IG, or SZC + IG on the excretion of potassium in the urine was observed after treatment (Figure 2). The results show that urine potassium excretion decreased in all three patient groups after treatment compared to the baseline. In SZC treatment group, the mean urine potassium excretion decreased from 59.10 ± 3.67 mmol/24 h at baseline to 52.20 ± 3.54 mmol/24 h after treatment (change of -6.9 mmol/24 h (95 % CI, 5.292 to 8.508); $p < 0.001$). In IG group, the average urine potassium excretion decreased from 59.30 ± 3.93 mmol/24 h at baseline to 58.50 ± 3.36 mmol/24 h after treatment (change of -0.80 mmol/24 h (95 % CI, -0.8736 to 2.474); p = 0.3433). Compared to the other two groups, SZC+ IG treatment group showed a significant decrease in average urine potassium excretion from 59.20 ± 3.65 mmol/24 h at baseline to 48.60 ± 3.16 mmol/24 h after treatment (change of -10.6 mmol/24 h (95 % CI, 9.21 to 11.99); $p < 0.001$). This indicates that SZC + IG has a stronger biological effect on potassium excretion in the urine compared to the other groups. The combination of SZC and IG is beneficial for maintaining normal blood potassium levels in the long term.

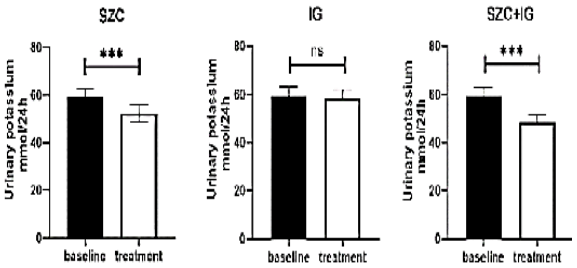

Figure 2: Urinary potassium excretion pre- and post-treatment with SZC, IG or SZC. ***Note:*** + IG. ***$P < 0.001$, and ns = not significant versus baseline

Urinary sodium excretion

After treatment with SZC, IG, or SZC + IG, there were no significant changes observed in urine sodium excretion. In SZC group with a concentration of 5 g/day, the average urine sodium excretion decreased from 35.40 ± 5.50 mmol/24 h to 34.10 ± 2.32 mmol/24 h, with $p > 0.01$. In IG treatment group, the urine sodium excretion also decreased from 35.60 ± 2.50 mmol/24 h to 35.50 ± 1.82 mmol/24 h, with $p > 0.01$. In SZC + IG treatment group, the average urine sodium excretion was 35.30 ± 2.15 mmol/24 h at baseline and 34.80 ± 2.82 mmol/24 h after combined treatment (Figure 3) and the difference was not statistically significant with $p > 0.05$. This indicates that the combination treatment of SZC with insulin and glucose infusion does not have a significant effect on urine sodium excretion.

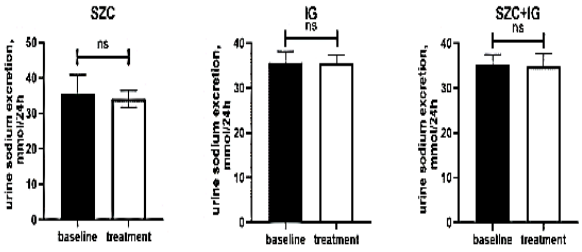

Figure 3: Urinary sodium excretion following treatment with SZC, IG or SZC+ IG

Other serum electrolytes

No clinically significant changes were observed in serum levels of calcium, magnesium, sodium, phosphate, ALT and albumin between the baseline and treatment groups during the study period. Results are shown in Tables 2 and Table 3.

Univariate analysis of patients' physical factors and outcomes

The result of the univariate analysis of patients' physical factors showed that patients' gender, age, occupation, marital status and other factors did not affect the maintenance of therapeutic effect of hyperkalemia. Also, diabetes, heart disease, infectious diseases and allergic diseases had no effect on the maintenance of efficacy. Interestingly, urban patients had better maintenance of blood potassium levels compared to rural patients. This observation leads to the hypothesis that antihypertensive medications may enhance the effectiveness of SZC used in the treatment.

DISCUSSION

Hyperkalemia is a common electrolyte disorder manifests as high blood potassium levels and causes arrhythmias, neuromuscular weakness and even death [1]. The Chinese National Medical Products Administration granted approval for SZC (sodium zirconium cyclosilicate) as a treatment for hyperkalemia in adults at the end of 2019 and it became commercially available in March, 2020. Sodium zirconium cyclosilicate is an inorganic crystal compound that effectively and stably lower blood potassium levels, with fast onset and minimal adverse reactions. It is not absorbed by the body and undergo cation exchange with potassium ions (K^+) by selectively binding to gastrointestinal potassium, thereby reducing serum potassium levels [13]. However, recent studies have shown that while blood potassium levels significantly decrease after 48 h of treatment with SZC, there is no significant effect within 4 h of treatment [15]. Insulin plus glucose infusion correct blood potassium within 15 min and is an effective intervention for acute hyperkalemia [4].

Table 2: Other serum electrolytes after treatment compared with the baseline

Outcome	SZC (n=40)	IG (n=38)	SZC+ IG (n=48)
Calcium (mg/dL)			
Baseline (Day 4)	9.56 (0.23)	9.76 (0.37)	9.31 (0.30)
Day 10	9.57 (0.27)	9.87 (0.39)	9.40 (0.33)
Changes from baseline, %(SD)	95% CI (-0.135-0.115)	95% CI (-0.272- 0.0519)	95% CI (-0.233- 0.0527)
P-value	0.8738	0.1792	0.2119
Magnesium (mg/dL)			
Baseline (Day 4)	2.62 (0.16)	2.56 (0.17)	2.73 (0.21)
Day 10	2.55 (0.14)	2.53 (0.15)	2.62(0.19)
Changes from baseline, % (SD)	95% CI (-0.0409-0.181)	95% CI (-0.0828-0.143)	95% CI (-0.0109-0.231)
P-value	0.2118	0.5967	0.0737
Phosphate (mg/dL)			
Baseline (Day 4)	4.12 (0.42)	4.02 (0.39)	4.07 (0.38)
Day 10	4.23 (0.44)	4.13 (0.4)	4.08 (0.4)
Changes from baseline, % (SD)	95% CI (-0.325-0.105)	95% CI (-0.318-0.0978)	95% CI (-0.215-0.195)
P-value	0.3103	0.2940	0.9228

Note: Baseline, as used in this study, refers to the final outcome measured before the initiation of the treatment. All values are reported as mean ± SD

Table 3: Alt and albumin content after treatment compared with the baseline

Indicator/group	SZC	IG	SZC+ IG
ALT (U/L)			
Baseline (Day 4)	24.3 (1.03)	24.4 (1.37)	24.1 (1.36)
Day 10	24.4 (2.44)	25.6 (1.03)	24.9 (1.22)
Changes from baseline, %(SD)	95% CI (-1.04-0.836)	95% CI (-1.59-0.389)	95% CI (-1.79-0.187)
P-value	0.8316	0.2298	0.1103
Albumin, %			
Baseline (Day 4)	54 (4.16)	56 (4.21)	55 (4.32)
Day 10	56 (5.02)	56 (4.08)	54 (5.11)
Changes from baseline, %(SD)	95% CI (-4.30-0.304)	95% CI (-4.07-0.0721)	95% CI (-1.36-3.36)
P-value	0.0877	0.0582	0.4011

Note: Baseline, as used in this study, refers to the final outcome measured before the initiation of the treatment. All values are reported as mean ± SD

Table 4: Univariate analysis of patient physical factors and parameters (n (%))

Variates	Success	Failure	t/X^2	*P*-value
Gender			0.02264	0.8804
Female	60 (52.2)	6 (54.5)		
Male	55 (47.8)	5 (45.5)		
Age	58.32	57.48		
Occupation			0.02025	0.8868
Student	4 (3.4)	0		
Staff	8 (6.8)	1 (11.1)		
Teacher	13 (11.1)	1 (11.1)		
Medical staff	27 (23.1)	1 (11.1)		
Cadre, retired	45 (38.5)	4 (44.4)		
Other	20 (17.1)	2 (22.2)		
Marital status			0.04811	0.8264
Married	97 (84.3)	9 (81.8)		
Unmarried	18 (15.7)	2 (18.2)		
Residence				
City	87 (89.7)	3 (10.3)	68.87	< 0.001***
Village	10 (10.3)	26 (89.7)		
Hypertension			18.97	< 0.001***
Yes	76 (70.4)	11 (61.1)		
No	32 (29.6)	7 (38.9)		
Diabetes			0.3099	0.5777
Yes	45 (44.6)	17 (68)		
No	56 (55.4)	8 (32)		
Heart disease			0.3361	0.5621
Yes	80 (74.8)	13 (68.4)		
No	27 (25.2)	6 (31.6)		
Infection			2.149	0.1427
Yes	84 (70.6)	6 (85.7)		
No	35 (29.4)	1 (14.3)		
Allergy			3.510	0.0610
Yes	79 (78.2)	15 (60)		
No	22 (21.8)	10 (40)		

Therefore, the combination of SZC and insulin plus glucose infusion has the advantage of fast onset and prolonged effect. This research evaluated the effectiveness and safety of three potassium-lowering agents in maintaining normal blood potassium levels within 4 h of initial treatment. In comparison with SZC and IG groups, SZC + IG treatment group had a higher proportion of severe hyperkalemia and higher blood potassium levels before treatment. However, SZC + IG treatment group displayed a significantly higher rate of patients attaining normal blood potassium levels after treatment, surpassing the other groups. Over the 30-day treatment period, SZC + IG group had a significantly increased likelihood of maintaining blood potassium levels within the normal range compared to SZC group and IG group, indicating that SZC+IG has the best treatment efficacy for hyperkalemia.

Limitations of this study

The sample size was only 126. A larger sample size and a longer study period are required to ensure the accuracy of this research outcomes. In clinical practice, clinical data within 4 h after medication are often not recorded and saved for many patients, which is a major reason for the small sample size in this study.

CONCLUSION

The combination of SZC and IG mitigates the high potassium levels in hyperkalemia and further ensures the achievement of normal blood potassium levels, demonstrating good short-term and long-term therapeutic effects. Additionally, the combination of SZC and IG does not exhibit significant adverse reactions, suggesting that it has a safety advantage. Future research, will require increasing patient population and extending the study duration to assess patient tolerance to this treatment approach.

DECLARATIONS

Acknowledgements

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Funding

None provided.

Ethical approval

This study has been approved by the Ethics Committee of the First Affiliated Hospital of the Third Military Medical University of Chinese PLA (approval no. Lun Shen 2023 Yan no. 0384).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors of this article declare that they bear the responsibility for the research conducted and the content of this work. Any liabilities and claims relating to the content of this article will be assumed by the authors named herein. The study was conceived and designed by Xuansheng Wu and Li Le. They also drafted the manuscript. The collection, analysis and interpretation of the experimental data were performed by Na Yin and Feng Dai. Xuansheng Wu, Li Le and Fang He contributed to the revision of the manuscript for important intellectual content. Xuansheng Wu and Li Yue contributed equally to this work. All authors have read and approved the final version of the manuscript.

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