

Efficacy and safety of polystyrene sulfonates for the treatment of hyperkalaemia in hospitalised adult patients; a scoping review

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ABSTRACT

Sodium and calcium polystyrene sulfonate (SPS and CPS) are potassium-binding resins frequently prescribed in the management of hyperkalaemia. We conducted a scoping review to examine the efficacy and safety of polystyrene sulfonates in hospitalised adults with hyperkalaemia and to identify knowledge gaps relevant to clinical practice. This scoping review was conducted following the PRISMA-ScR guidelines. Studies were eligible for inclusion if they reported on the use of SPS or CPS in hospitalised adults for the treatment of hyperkalaemia. Searches were conducted on Medline (PubMed) and the Web of Science Core Collection. The protocol was prospectively registered with the Open Science Framework. In this study, seventeen studies were included, representing 31 treatment arms and 4325 hospitalised adult patients. Overall, the mean baseline serum potassium concentration was 5.8 ± 0.28 mmol/L, with a mean reduction of approximately 1.0 mmol/L. No significant difference was observed between SPS and CPS (0.98 mmol/L versus 0.95 mmol/L; $P = 0.829$). The median time to nadir serum potassium was 12.5 hours. A moderate negative correlation was observed between polystyrene sulfonate dose and the change in serum potassium concentration ($r = -0.462$, $P = 0.010$). SPS dose was significantly correlated with potassium reduction ($r = -0.457$, $P = 0.019$), while CPS was not ($r = -0.515$, $P = 0.485$). Constipation was the most common gastrointestinal adverse event, occurring most frequently in patients who received CPS. Hyponatraemia, hypocalcaemia and hypoglycaemia were observed only in SPS-treated patients, whereas hypercalcaemia occurred exclusively in those treated with CPS. In this study, we concluded that polystyrene sulfonates showed a modest reduction in serum potassium concentrations in patients who had mild hyperkalaemia regardless of resin type. While gastrointestinal and metabolic adverse events were uncommon, the specific side effects varied according to the type of resin used.

Implication for health policy/practice/research/medical education:

This scoping review of real-world data demonstrates that polystyrene sulfonates effectively reduce serum potassium concentrations in hospitalised patients with mild hyperkalaemia, with no observed differences in efficacy between sodium and calcium formulations. Gastrointestinal and metabolic adverse events were generally uncommon and appeared to vary according to resin type, while bowel-related complications were rare and may be disproportionately emphasised in the literature. Considering the prohibitive costs and limited availability of newer potassium binders, such as patiomer and sodium zirconium cyclosilicate, particularly in low- and middle-income countries, polystyrene sulfonates remain a safe, accessible, and effective therapeutic option for the management of hyperkalaemia.

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Introduction

Potassium is the most abundant cation in the human body and is primarily confined to the intracellular compartment. The equilibrium between intracellular and extracellular potassium concentrations is critical for

the resting membrane potential and consequently affects muscle contractility and nerve conduction. Changes in serum potassium levels can lead to muscle weakness and life-threatening cardiac arrhythmias (1,2).

Hyperkalaemia, defined as a serum potassium

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concentration ($[K^+] \geq 5.5$ mmol/L), is a potentially life-threatening electrolyte disorder in hospitalised patients. Hyperkalaemia is frequently asymptomatic; but it may cause fatigue, muscle weakness, and cramps, and rarely paralysis. Risk factors for hyperkalaemia include chronic kidney disease, heart failure, diabetes mellitus, and drugs that interfere with renal potassium excretion (3,4). Since the 1950s, polystyrene sulfonates, sodium (SPS) and calcium (CPS), have been used in treatment of hyperkalaemia by facilitating gastrointestinal potassium elimination (4,5). Despite their widespread use, the clinical value for SPS and CPS remains questionable due to efficacy and safety concerns. A 2020 systematic review reported limited high-quality evidence supporting SPS/CPS use, particularly in acute inpatient settings (6). Nonetheless, SPS remains widely prescribed, with 85% of surveyed specialists continuing to use it despite having 88% awareness of the associated risks (6). Due to the lack of consensus and ongoing use of SPS/CPS therapies, this scoping review aims to evaluate the current literature on the efficacy and safety of SPS and CPS in hospitalised adult patients with hyperkalaemia.

Objectives

We conducted a scoping review to map the existing research regarding the efficacy and safety of polystyrene sulfonates, which may assist in guiding future research on the utilisation of polystyrene sulfonates for the treatment of hyperkalaemia in the hospitalised patient. The following research questions were investigated:

1. How effective are polystyrene sulfonates in the treatment of hyperkalaemia in hospitalised patients?
2. How long does it take for the $[K^+]$ to reach the nadir value?
3. Is there a dose related response when using polystyrene sulfonates?
4. Are there any differences between SPS and CPS regarding efficacy and safety?
5. What are the adverse effects of polystyrene sulfonate?

Materials and Methods

Study design and registration

This scoping review was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR). The study protocol was registered on the Open Science Framework in September 2024 (<https://osf.io/7xhmb>).

Eligibility

Included research articles that reported on the use of SPS or CPS in the treatment of hyperkalaemia among hospitalised adult patients, aged 18 years and older. Eligible studies included randomised controlled trials, prospective and retrospective cohort studies, quasi-experimental studies, and case series. Case reports, paediatric studies, animal

studies, and studies performed in outpatient settings were excluded.

Information sources and search strategy

To identify appropriate data, literature search was conducted in Medline (PubMed) and the Web of Science Core Collection databases. The search strategy was performed by one of the authors (MYC), with adaptations made to suit the syntax of each database. Conference proceedings of major nephrology congresses from the past three years were also screened, including International Society of Nephrology's World Congress of Nephrology, the American Society of Nephrology's Kidney Week, and the European Renal Association congress. Reference lists of relevant systematic reviews were also used to identify additional articles missed by the original database search.

Search strategy of database titles

Medline (PubMed)

#1 "Hyperkalemia" [MeSH] OR hyperkalemia [Title/Abstract] OR hyperkalaemia [Title/Abstract] OR "hyperpotassaemia" [Title/Abstract] OR "hyperpotassemia" [Title/Abstract] Filters: from 1950 – 2024

#2 (Sodium polystyrene sulfonate [Mesh] OR Sodium polystyrene sulfonate [Title/Abstract] OR sodium polystyrene sulfonate [Title/Abstract] OR Calcium polystyrene sulfonate [Mesh] OR calcium polystyrene sulfonate [Title/Abstract] OR calcium polystyrene sulfonate [Title/Abstract]) AND Filters: from 1950 – 2024
#1 and #2

Web of Science

#1 TS= "hyperkalaemia" OR TS= "hyperkalemia" OR TI= "hyperkalaemia" OR TI= "hyperkalemia" OR AB= "hyperkalaemia" OR AB= "hyperkalemia"

#2 TS="sodium polystyrene sulfonate" OR TS="calcium polystyrene sulfonate" OR TI="sodium polystyrene sulfonate" OR TI="calcium polystyrene sulfonate" OR AB="sodium polystyrene sulfonate" OR AB="calcium polystyrene sulfonate"
#1 AND #2

Study selection

The search results were imported into Rayyan software (<https://www.rayyan.ai/>) for screening and removal of duplicates. Two reviewers (NM and MYC) screened all identified article titles and abstracts. Full text reviews were conducted on potentially eligible studies. Conflicts regarding the articles were resolved by consensus.

Data extraction

The first reviewer (NM) developed a data extraction tool in Excel. Data extraction for included studies was performed by a single reviewer (NM) and independently cross-checked by a second reviewer (MYC). The extracted data included study design, type of publication, year of

publication, study setting, sample size, demographic data, $[K^+]$ at baseline and at follow-up, duration of the follow-up period, difference in $[K^+]$ from baseline to the nadir value, time to reach nadir value, comorbidities including hypertension, diabetes mellitus, and heart and kidney disease, and documented adverse events.

Synthesis of results

We provided a narrative synthesis of the extracted data. This was displayed in a table format. A narrative discussion was used to compare similarities and differences between studies.

Results

Selection of included studies

The literature search yielded 204 studies, and 22 duplicates were removed. Of the remaining 182 records screened, 164 were excluded as per exclusion criteria. A total of 17 articles were included in the scoping review (7-23). The flow diagram is shown in Figure 1.

Characteristics of included studies

Study designs

Most of the studies, 10/17 (59%), were retrospective cohort designs, with 6/17 (35%) being prospective observational, and 1/17 (6%) study was quasi-experimental.

Country distribution

Most publications emanated from North America with 10/17 studies, followed by 5/17 studies from Asia, and 2/17 from Europe. The search strategy yielded no studies from Africa. The years of publication ranged from 2011 to 2024, with the highest frequency of publications observed in 2023.

Study population

The 17 included articles comprised of 31 treatment arms. Most studies, 9/17 (53%) had two or more treatment arms. Of the studies with multiple treatment arms, six articles had two treatment arms, two articles had four treatment arms, and one had three treatment arms. Almost all

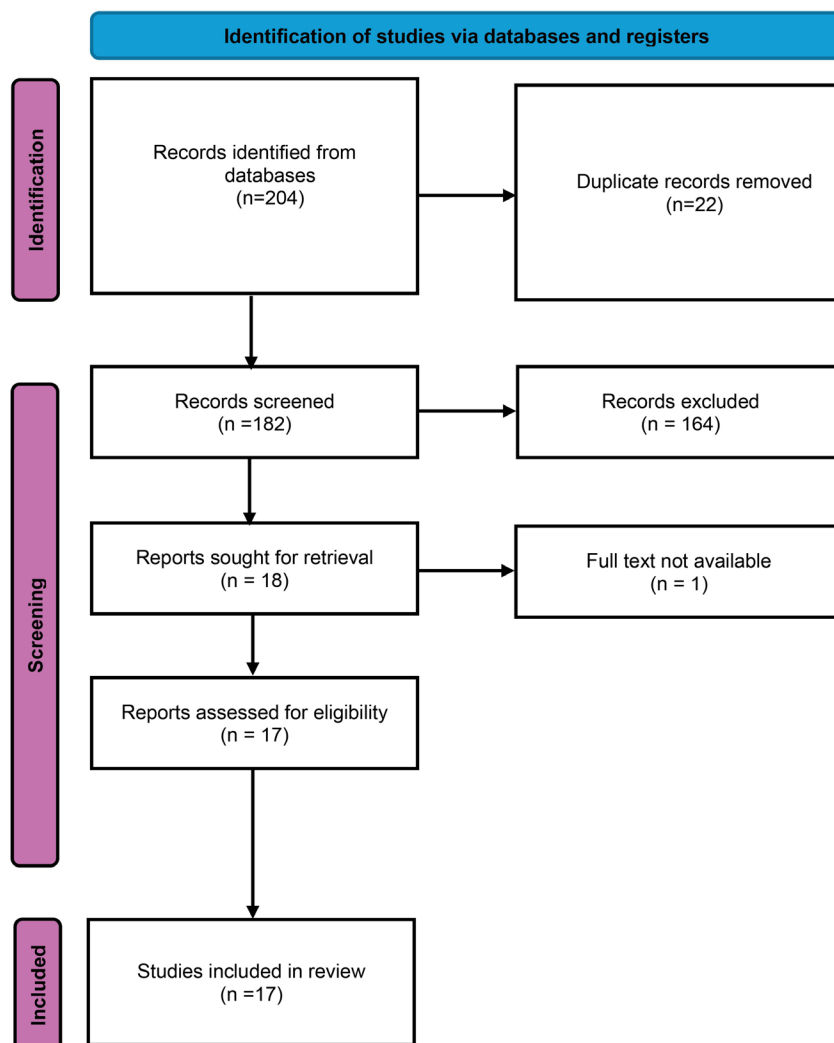


Figure 1. Flow diagram of study selection.

studies, 16/17 (94%), were full-text peer-reviewed articles, with only one being a conference abstract. Sample sizes ranged from 33 to 2350 patients per study.

The total pooled sample size was 4325 patients across the 31 treatment arms. Sex was reported for 3883/4325 (89.8%) patients, of whom 2132 (54.9%) were male and 1751 (45.1%) female (male-to-female ratio 1.22:1). The mean age was 67.2 years, with a range of 52–79 years. The characteristics of included studies are shown in Table 1.

Definition of hyperkalaemia

Most studies defined hyperkalaemia as $[K^+] \geq 6.0$ mmol/L ($n=15$, 88%) (Table 1).

Comorbidities

The most common comorbidity was kidney disease, reported in 16/17 (94%) studies, affecting 3746 (86.6%) patients. Acute kidney injury was found in 662 (15.3%) of

patients with kidney disease, while 314 (7.3%) had kidney failure on dialysis. Serum creatinine was reported in 12/17 (71%) studies, with a median value of 206 (IQR 180–271) $\mu\text{mol/L}$. Heart failure was reported in 13/17 (76%) studies, affecting 1056 (24.4%) patients, followed by diabetes mellitus, reported in 10/17 (59%) studies, with 410 (9.5%) patients involved. The least common comorbidity was hypertension, found in 6/17 (35%) studies, involving 322 (7.4%) patients (Table 2).

How effective are polystyrene sulfonates in the treatment of hyperkalaemia in hospitalised patients?

The overall baseline serum potassium values were reported in 31 treatment arms, with a mean value of 5.8 ± 0.3 mmol/L, and a range of 5.3–6.5 mmol/L. Follow up serum potassium levels were also available in all 31 study arms, with an overall mean value of 4.8 ± 0.2 mmol/L and a range of 4.5–5.5 mmol/L (Figure 2a).

Table 1. Summary of selected studies characteristics

Items	Frequency
Study designs	
Retrospective observational	10
Prospective observational	6
Quasi-experimental	1
Country	
United States	9
Japan	3
China	1
United Kingdom	1
South Korea	1
Russia	1
Canada	1
Publication year	
2011	1
2014	1
2015	1
2017	1
2018	3
2019	1
2021	2
2022	1
2023	5
2024	1
Publication type	
Journal articles	16
Conference abstract	1
Sample size distribution	
Minimum	11
Maximum	1060
Median sample size (IQR)	61 (29–112)
Definition of hyperkalaemia	
≥ 5.0 mmol/L	2
≥ 6.0 mmol/L	15

Abbreviation: IQR, interquartile range.

Table 2. Summary of demography, comorbidities, medication, and additional therapies for hyperkalaemia

Variables	
Number of treatment arms	31
Total sample size, n%	4325 (100)
Demographic data	
Age (years), mean $\pm$ SD	67.2 $\pm$ 6.9
Male, n%	2132 (54.9) ^a
Female, n%	1751 (45.1) ^a
Comorbidities, n	
Hypertension, n%	322 (7.4)
Heart failure, n%	1056 (24.4)
Diabetes mellitus, n%	410 (9.5)
Kidney disease, n%	3746 (86.6)
Kidney failure on dialysis, n%	314 (7.3)
Acute kidney injury, n%	662 (15.3)
Kidney transplant recipients, n%	6 (0.1)
Serum creatinine ($\mu\text{mol/L}$), median (IQR)	206 (180–271)
Medication	
RAASi (including ACEi, ARB and spironolactone), n%	971 (22.4)
Trimethoprim, n%	185 (4.3)
Potassium supplementation, n%	153 (3.5)
Beta-blockers, n%	92 (2.1)
Calcineurin inhibitors, n%	57 (1.3)
NSAIDs, n%	27 (0.6)
Additional therapies for hyperkalaemia	
Beta-2 agonist, n%	588 (13.6)
Insulin, n%	500 (11.6)
Diuretics, n%	395 (9.1)
Sodium bicarbonate, n%	253 (5.8)

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; NSAIDs, non-steroidal anti-inflammatory drugs.

^a Percentages calculated from the 3883 patients with sex reported for the SPS/CPS-treated population.

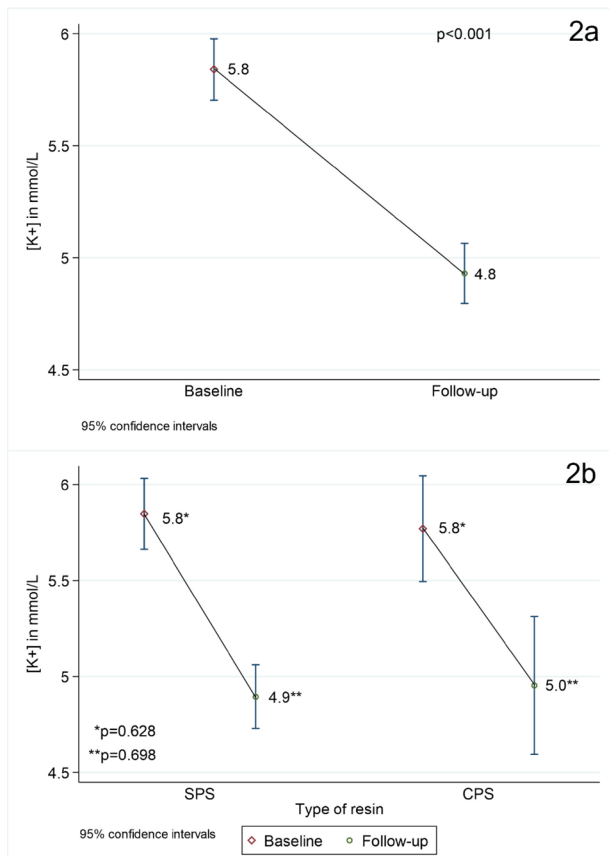


Figure 2. (a) Baseline and follow-up potassium levels for all included studies. [K⁺], serum potassium concentration. (b) A comparison of the absolute serum potassium concentrations between SPS and CPS at baseline and following treatment. Abbreviations: SPS, sodium polystyrene sulfonate; CPS, calcium polystyrene sulfonate; [K⁺], serum potassium concentration.

How long did it take for the serum potassium concentration to reach the nadir value?

Time to nadir potassium was reported in 17/31 (55%) treatment arms. The median time in the nadir [K⁺] was 12.5 (IQR 10–15) hours.

Was there a dose-response relationship when using polystyrene sulfonates?

A moderate negative correlation was observed between polystyrene sulfonate dose and the change in [K⁺], with Pearson's $r = -0.462$, $P = 0.010$ (Figure 3). SPS was the most frequently used intervention, found in 26/31 (84%) arms ($n = 3858$), while CPS was used in 5/31 (16%) arms ($n = 467$). The average combined SPS/CPS dose was 28 g.

Were there any differences between SPS and CPS regarding efficacy?

An overall mean dose of SPS was 28.5 g, compared to 25.2 g for CPS. At baseline and following treatment, there were no statistically significant differences regarding the absolute [K⁺]s between SPS and CPS (Figure 2b). There was also no difference in the absolute reduction in [K⁺]

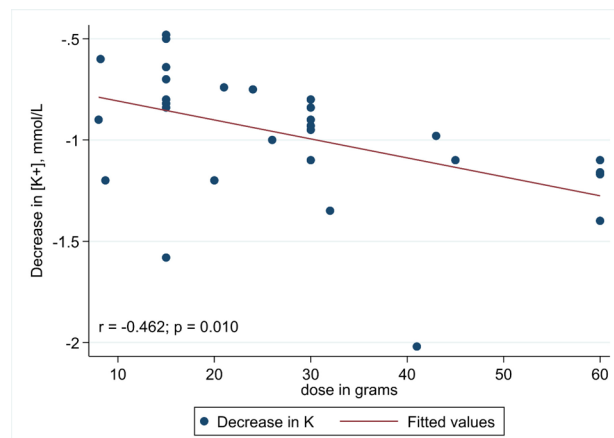


Figure 3. Correlation between polystyrene sulfonate (SPS and CPS) dose and the reduction in the serum potassium concentration. Abbreviations: SPS, sodium polystyrene sulfonate; CPS, calcium polystyrene sulfonate; [K⁺], serum potassium concentration.

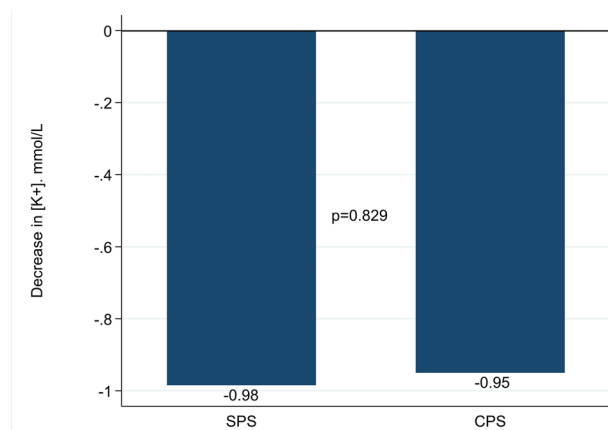


Figure 4. A comparison of the reduction in the serum potassium concentration between SPS and CPS. Abbreviations: SPS, sodium polystyrene sulfonate; CPS, calcium polystyrene sulfonate; [K⁺], serum potassium concentration.

when comparing SPS and CPS (Figure 4). A statistically significant moderate inverse correlation was found between SPS dose and the reduction in [K⁺] ($r = -0.457$, $P = 0.019$). Although a similar moderate inverse correlation was observed with CPS dose ($r = -0.515$), it was not statistically significant ($P = 0.485$; Figure 5).

What were the adverse effects of polystyrene sulfonate?

Adverse events were variably reported across the included studies. We categorised the adverse effects into gastrointestinal and metabolic complications.

Gastrointestinal adverse events

The total sample size of studies reporting gastrointestinal adverse events was 2129 with 1847 in SPS treated patients and 282 in those who received CPS. Overall, 202/2129 (9.5%) of patients developed gastrointestinal adverse events. Constipation was the most frequent affecting a

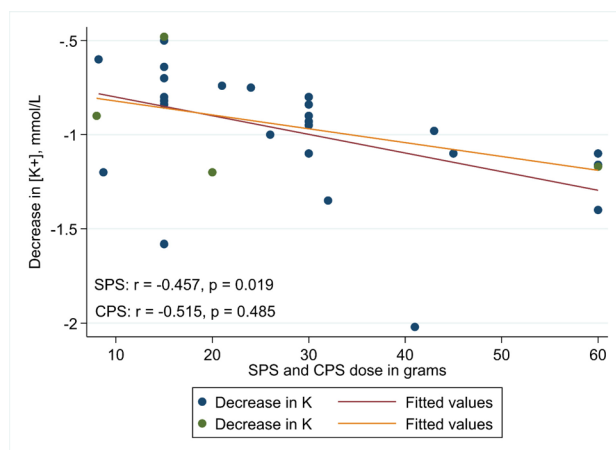


Figure 5. Correlation between the dose of SPS and CPS and the reduction in the serum potassium concentration. Abbreviations: SPS, sodium polystyrene sulfonate; CPS, calcium polystyrene sulfonate; [K⁺], serum potassium concentration.

total of 156 (7.3%) patients. This was followed by nausea and vomiting involving 30 (1.4%) patients. Although less frequent, more serious complications were also observed: gastrointestinal ulceration occurred in seven (0.3%), bowel necrosis affected only three (0.14%) patients, intestinal colitis affecting four patients; and bowel perforation and ischaemia affecting one patient each (0.05%) and occurred exclusively with SPS (Table 3).

Metabolic adverse events

The total sample size of studies reporting metabolic adverse events was 1027 with 802 in SPS treated patients and 225 in those who received CPS. Overall, 288/1027 (28%) patients developed metabolic adverse events, with

hypomagnesaemia occurring in 82 patients (8%), followed by hypernatraemia in 77 (7.5%), hypocalcaemia in 70 (6.8%) and hypokalaemia in 42 (4.1%). Hypoglycaemia and hypercalcaemia were rare. When comparing SPS and CPS, all episodes of hypernatraemia (77/802, 9.6%), hypocalcaemia (70/802, 8.7%) and hypoglycaemia (13/802, 1.6%) occurred in patients treated with SPS, whereas all cases of hypercalcaemia (4/225, 1.8%) were observed in those who received CPS (Table 3).

Adjunctive therapies for hyperkalaemia

Insulin was used in 7/31 treatment arms (23%), involving 500 patients (11.6%). Beta-2 agonists were administered in six arms (19%), including 588 patients (13.6%), while sodium bicarbonate was reported in seven arms (23%), including 253 patients (5.8%), and diuretics were used in six arms (19%), involving 395 patients (9.1%). Laxative use was noted in one arm (3%), although the number of patients was not specified. A greater proportion of patients who received CPS were treated with adjunctive therapies in all categories (Figure 6).

Discussion

Overall, both SPS and CPS were effective in lowering serum potassium, with a mean reduction of approximately 1.0 mmol/L. This is consistent with findings from Wong et al, who reported a reduction greater than 0.5 mmol/L in 88% of studies included in their systematic review. Wong et al also identified three studies as having a low risk of bias and reported the reduction in [K⁺] to range from 0.14 to 1.04 mmol/L (6). In our cohort, baseline serum potassium levels were within the mild hyperkalaemia range. Most of the included studies also had baseline [K⁺] below 6.0

Table 3. Gastrointestinal and metabolic adverse effects in the overall study population and stratified by type of polystyrene sulfonate

Sample size of studies reporting gastrointestinal adverse events	All N=2129, n (%)	SPS N=1847, n (%)	CPS N=282, n (%)
Constipation	156 (7.3)	123 (6.7)	33 (11.7)
Nausea and vomiting	30 (1.4)	26 (1.4)	4 (1.4)
Ulceration	7 (0.3)	7 (0.4)	0
Intestinal colitis	4 (0.2)	4 (0.2)	0
Bowel necrosis	3 (0.1)	3 (0.16)	0
Bowel perforation	1 (0.05)	1 (0.05)	0
Bowel ischaemia	1 (0.05)	1 (0.05)	0
Sample size of studies reporting metabolic adverse events	All N=1027, n (%)	SPS N=802, n (%)	CPS N=225, n (%)
Hypomagnesaemia	82 (8.0)	75 (9.4)	7 (3.1)
Hypernatraemia	77 (7.5)	77 (9.6)	0
Hypocalcaemia	70 (6.8)	70 (8.7)	0
Hypokalaemia	42 (4.1)	35 (4.4)	7 (3.1)
Hypoglycaemia	13 (1.3)	13 (1.6)	0
Hypercalcaemia	4 (0.4)	0	4 (1.8)

Abbreviations: SPS, sodium polystyrene sulfonate; CPS, calcium polystyrene sulfonate.

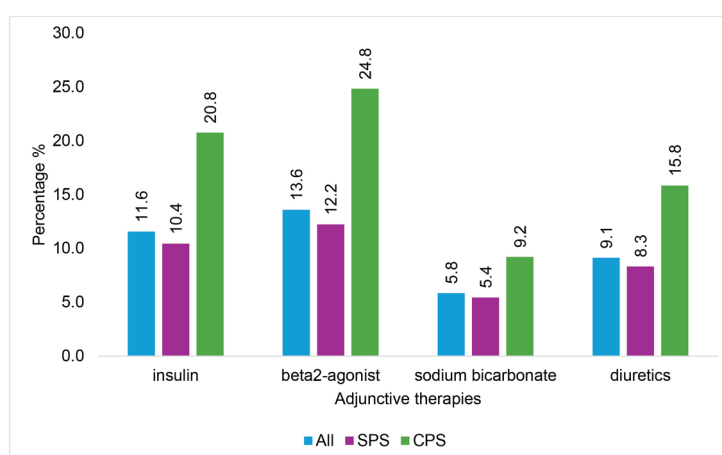


Figure 6. Comparison of the proportion of adjunctive therapies administered in the overall study population and stratified by type of SPS (sodium polystyrene sulfonate) and CPS (calcium polystyrene sulfonate).

mmol/L, like those in the systematic review. Therefore, although we observed a statistically significant reduction in serum $[K^+]$, the efficacy of SPS or CPS in patients with more severe hyperkalaemia remains uncertain.

We observed no significant difference in efficacy between SPS and CPS, despite similar baseline $[K^+]$'s. A moderate inverse correlation was noted between the dose of SPS/CPS and the reduction in $[K^+]$. Notably, a higher proportion of patients treated with CPS also received adjunctive therapies such as insulin, beta-2 agonists, sodium bicarbonate, and diuretics. This may have attenuated any differences in efficacy between the two resins, potentially indicating that SPS may be more effective.

We found that the median time to reach nadir $[K^+]$ was 12.5 hours, with a wide range from 6 hours up to 672 hours. In the study by Wong et al, only eight studies reported achieving nadir $[K^+]$ within 5–15 hours, while ten studies reported nadirs occurring after 72 hours. Given our findings and those of others (6), we recommend that polystyrene sulfonates should not be used alone in the management of symptomatic hyperkalaemia, as their onset of action, magnitude of effect and time to reach nadir potassium levels are unpredictable and highly variable.

Constipation was the most frequently reported gastrointestinal adverse effect and was notably more common among patients treated with CPS. This may be related to the interaction between calcium ions and the calcium-sensing receptors located within the gastrointestinal tract (24). Stool volume is a key determinant of the efficacy of polystyrene sulfonates. Emmett et al showed that the addition of phenolphthalein, a secretory laxative, to SPS enhanced potassium elimination via the stool (25). Thus, the higher rate of constipation in CPS-treated patients may partly account for the increased need for adjunctive therapies in this group.

Conversely, the addition of laxatives to SPS is not recommended due to the risk of colonic necrosis, as they

accelerate the transit and increase the concentration of SPS in the distal colon (24). This complication was rare in our study. In a large retrospective study, the absolute risk of colonic necrosis was only 0.14% with the number needed to harm of 1395 (26). Therefore, the risk of colonic necrosis is overemphasised.

Hypomagnesaemia was the most common metabolic disturbance observed with both SPS and CPS. Hyponatraemia and hypocalcaemia were more frequently associated with SPS, while hypercalcaemia was more prevalent in patients treated with CPS. Each gram of SPS contains 4 mmol of sodium. Given that the average dose used was ~30 g, the total sodium load per dose was around 120 mmol, which is theoretically available for exchange with potassium. Three previous studies have documented increases in serum sodium concentrations (25). The tendency of SPS to cause hypomagnesaemia and hypocalcaemia is due to its greater affinity for divalent cations (28). In contrast, CPS was associated with hypercalcaemia. Arroyo et al (27) reported few cases with only mild increases in serum calcium concentrations, while Sevit et al (29) noted that half of the patients treated with CPS developed asymptomatic hypercalcaemia.

Adjunctive treatments were more frequently reported in arms where patients presented with severe hyperkalaemia or underlying kidney disease; however, their use was not systematically reported across all studies.

Conclusion

This scoping review provides an overview of the current evidence on the use of SPS and CPS for the management of hyperkalaemia in hospitalised patients. Both agents showed modest reduction in serum potassium levels in patients who have mild hyperkalaemia. Although both gastrointestinal and metabolic adverse events were uncommon, specific side-effects were dependent on the type of polystyrene sulfonate. No publications from African settings were identified, despite widespread use

of SPS and CPS across the continent. This represents a considerable evidence gap, particularly in resource-limited settings, where alternative therapies may not be available.

Limitations of the study

Most of the studies were retrospective in design, lacking randomisation and therefore increasing risk of bias. There was also some heterogeneity in reporting, with variable potassium thresholds, follow-up intervals, and dosing regimens. The use of adjunctive therapy limits the ability to isolate the effect of SPS/CPS.

Authors' contribution

Conceptualization: Mogamat-Yazied Chothia.

Data curation: Ntombizodwa Mpungose.

Formal analysis: Mogamat-Yazied Chothia.

Investigation: Ntombizodwa Mpungose.

Methodology: Mogamat-Yazied Chothia.

Project administration: Ntombizodwa Mpungose.

Resources: Mogamat-Yazied Chothia and Ntombizodwa Mpungose.

Supervision: Mogamat-Yazied Chothia.

Validation: Mogamat-Yazied Chothia and Ntombizodwa Mpungose.

Visualization: Mogamat-Yazied Chothia.

Writing—original draft: Mogamat-Yazied Chothia and Ntombizodwa Mpungose.

Writing—review and editing: Mogamat-Yazied Chothia and Ntombizodwa Mpungose.

Ethical issues

As this study was a scoping review, there were no ethical issues. Additionally, other ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Conflicts of interest

The authors declare no conflicts of interest.

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