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WJMA mainly publishes articles reporting research results and findings obtained through meta-analysis and systematic review in a wide range of areas, including medicine, pharmacy, preventive medicine, stomatology, nursing, medical imaging, and laboratory medicine.

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Comprehensive analysis of sodium polystyrene sulfonate-induced colitis: A systematic review

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Abstract

BACKGROUND

Sodium polystyrene sulfonate (SPS) is commonly prescribed for the management of hyperkalemia, a critical electrolyte imbalance contributing to over 800000 annual visits to emergency departments.

AIM

To conduct a systematic review of documented cases of SPS-induced colitis and assess its associated prognosis.

METHODS

Following the PRISMA-P guidelines, our study employed Medical Subject Headings and Health Sciences Descriptors, skillfully combined using Boolean operators, to conduct comprehensive searches across various electronic databases, including Scopus, Web of Science, MEDLINE (PubMed), BIREME (Biblioteca Regional de Medicina), LILACS (Latin American and Caribbean Health Sciences Literature), SciELO (Scientific Electronic Library Online), Embase, and Opengray.eu. Language criteria were confined to English, Spanish, and Portuguese, with no limitations on the publication date. Additionally, we manually scrutinized the reference lists of retrieved studies. To present our findings, we utilized simple descriptive analysis.

RESULTS

Our search strategy yielded a total of 442 references. After rigorous evaluation, we included 51 references, encompassing 59 documented cases of colitis. Predominant clinical presentations included abdominal pain, observed in 35 (60.3%) cases, and bloating, reported in 18 (31%) cases. The most frequently affected sites of inflammation were the cecum, rectum, and small intestine, accounting for 31%, 25.8%, and 22.4% of cases, respectively. Colonoscopy findings were described in 28 (48.2%) cases, and 29 (50%) of patients required surgical intervention. Among the subset of patients for whom outcome data was available, 39 (67.2%) experienced favorable outcomes, while 12 (20.6%) unfortunately succumbed to the condition. The mean time required for resolution was 36.7 d, with a range spanning from 1 to 120 d.

CONCLUSION

SPS demonstrates the capacity to effectively lower serum potassium levels within 24 h. However, this benefit is not without the risk of bowel injury. Our study highlights the absence of high-quality data pertaining to the incidence of adverse events associated with SPS usage, making it challenging to determine whether the potential risks outweigh the benefits. However, a significant mortality rate related to SPS-induced colitis was noted. Future investigations should prioritize randomized controlled trials with a sufficiently large patient cohort to ascertain the true utility and safety profile of this medication.

Key Words: Sodium polystyrene sulfonate; Hyperkalemia; Colitis; Bowel necrosis; Kayexalate

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Core Tip: Our systematic review on sodium polystyrene sulfonate (SPS)-induced colitis underscores the critical need for a comprehensive understanding of the associated risks. While SPS effectively addresses hyperkalemia, our findings reveal a notable incidence of bowel injury. With limited high-quality data available, the balance between benefits and risks remains unclear. Future research, particularly randomized controlled trials, is essential to determine the true utility and safety profile of SPS in clinical practice.

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INTRODUCTION

Adverse drug events span a broad spectrum of clinical presentations, affecting various organ systems. Recognizing and understanding these medication-related effects is essential for mitigating associated morbidity and mortality[1]. Sodium Polystyrene Sulfonate (SPS) has found a specific niche in the management of hyperkalemia, a life-threatening electrolyte disturbance that leads to over 800000 emergency department visits annually[2]. This therapeutic agent gained approval from the United States Food and Drug Administration (FDA) in 1958, four years prior to the implementation of the Kefauver-Harris Drug Amendments, legislation designed to ensure drug efficacy and safety[3].

The effective management of hyperkalemia is of paramount importance for preserving life, as it serves as a protective barrier against potentially fatal arrhythmias by either facilitating potassium translocation from the serum into cells or enhancing renal potassium excretion[4]. SPS, a cation exchange resin, can be administered orally or rectally, primarily exerting its effects within the colon by facilitating the exchange of sodium ions for potassium ions[1,4,5]. Nevertheless, it is crucial to note that this drug is not without its share of side effects[6]. Historically, it has been co-administered with sorbitol, an osmotic laxative, to mitigate the risk of severe constipation or fecal impaction, which can occur when SPS is administered in isolation[1]. The FDA, in 2009, issued a black box warning to underscore the heightened risk of intestinal necrosis associated with this combination therapy[3].

Typically, gastrointestinal adverse effects manifest as mild symptoms, such as nausea and constipation[7]. However, more severe and potentially fatal complications, including colonic ulceration, severe colitis, and necrosis, have been linked to SPS therapy[7,8]. Notably, the severity of these complications tends to correlate with the overall clinical condition of patients, particularly those with a history of organ transplantation, chronic kidney failure, or individuals in the postoperative period[4].

One of the most widely accepted theories regarding the mechanism of injury revolves around the presence of renin in high concentrations among patients with renal failure. The activation of renin and subsequent splanchnic vasoconstriction may lead to non-occlusive mesenteric ischemia, predisposing the colonic mucosa to injuries and electrolyte disturbances. However, it remains unclear why patients with renal failure are more susceptible to this catastrophic complication. It is possible that they are more prone to hyperkalemia, necessitating higher doses of SPS treatment than

other patient groups[4].

Typically, the colon represents the gastrointestinal tract most frequently affected by SPS-induced complications. These lesions necessitate endoscopic or colonoscopic analysis with biopsy to rule out differential pathologies such as cancer. While gastric involvement is less common, it was identified in only two cases in our comprehensive review. Biopsy results typically reveal intestinal necrosis, ulcers, or perforations, with more than 90% of tissue samples exhibiting an accumulation of SPS crystals. The presence of kayexalate crystals in pathology specimens distinguishes kayexalate-induced necrosis from ischemic necrosis. Histological evidence of angulated crystals of sodium polystyrene sulfate in areas of mucosal erosions, ulcerations, or frank necrosis strongly suggests the diagnosis. Additional related findings include inflammatory exudates, pseudomembrane formation, and acute/chronic serositis. These crystals are typically identified adhered to the mucosa or embedded within the inflammatory milieu and ulcerations. Thus, in reaching a diagnosis, it is imperative to rule out conditions that can mimic SPS-induced effects, such as neoplasms, inflammatory diseases, and infectious diseases[4].

The objective is to conduct a systematic review of documented cases of SPS-induced colitis and to assess the overall prognosis associated with this condition.

MATERIALS AND METHODS

Methods

This study was carried out under the recommendations contained in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines[9]. Our systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO), maintained by York University (CRD42022265756).

Data sources

Studies were retrieved using the terms described in [Supplementary material](#). Searches were run in January 2021 on the electronic databases Scopus, Web of Science, MEDLINE (PubMed), BIREME (Biblioteca Regional de Medicina), LILACS (Latin American and Caribbean Health Sciences Literature), SciELO (Scientific Electronic Library Online), Embase and Opengray.eu. There was no date of publication restrictions. The reference lists of the retrieved studies were submitted to manual search. Authors were contacted when full text was not found.

Inclusion criteria and outcomes

Case report or case series studies were eligible for selection. If there was more than one study published using the same case, the most recent study was selected for analysis. Studies published only as abstracts were included, as long as the data available made data collection possible. Studies written in languages other than English, Spanish, French or Portuguese were excluded.

Study selection and data extraction

An initial screening of titles and abstracts was the first stage to select potentially relevant papers. The second step was the analysis of the full-length papers. Two independent reviewers (GPA and GFR) extracted data using a standardized form after assessing and reaching consensus on eligible studies. The same reviewers separately assessed each study and extracted data about the characteristics of the subjects and the outcomes measured. A third reviewer (LGB) was responsible for clearing divergences in study selection and data extraction.

Quality assessment

Methodological quality assessment of case reports and case series was performed by two independent authors (GPA and GFR) using the tool presented by Murad *et al*[10]. Divergences were discussed with a third reviewer (LGB) until consensus was reached. Since questions 5 and 6 of the original tool are mostly relevant to cases of adverse drug events, we modified them to better suit the cases of polystyrene-induced colitis. Therefore, we considered question 5 as 'was there gastrointestinal damage in the case of reexposure?' and question 6 as 'was there a temporal relationship between exposure and outcome?'.

Statistical analysis

Simple descriptive statistics, such as the mean and standard deviation (SD), frequency, and median were used to characterize the data. Data were summarized using RStudio (version 4.0.2).

RESULTS

Search and selection process

A systematic search yielded a total of 442 references, from which 203 duplicates were excluded. Subsequently, a meticulous evaluation of titles and abstracts led to the exclusion of 169 references. A total of 69 full-text papers underwent thorough analysis. In the final phase, 51 references, encompassing a total of 59 cases, were included in the study. The search process is visually depicted in [Figure 1](#). The inclusion criteria for studies were either case reports or case series.

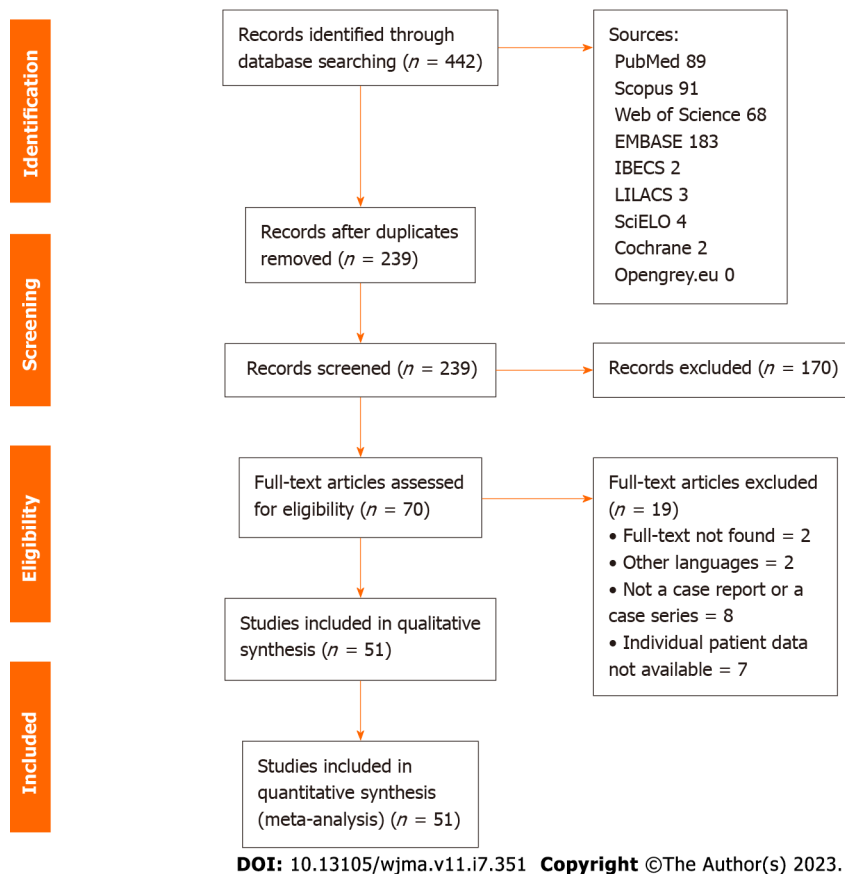


Figure 1 PRISMA flow diagram.

Geographical distribution and baseline characteristics

The distribution of cases across different regions revealed that the United States of America (USA), India, Canada, and Thailand accounted for the majority, with proportions of 48.2%, 10.3%, 6.9%, and 5.1%, respectively. Table 1 presents the baseline characteristics of the included cases. Among the 59 patients, 34 (58.6%) were male. The age spectrum encompassed individuals from less than 1 year old to 89 years old, with a mean age of 60.6 years. All patients received a diagnosis of SPS-induced colitis. The predominant type of polystyrene was sodium (Kayexalte) in 47 (81%) patients, while calcium (Kalimate) polystyrene was administered to 11 patients, with a mean dose of 83.6 g administered orally in the 38 cases where the dose was reported. It is noteworthy that all cases included in the analysis were derived from publications in medical journals.

Clinical presentation

Abdominal pain and bloating were the most prevalent clinical presentations, observed in 35 (60.3%) and 18 (31%) cases, respectively. Hematochezia, constipation, and diarrhea followed, with frequencies of 29.3%, 12%, and 12%, respectively. A smaller proportion, 6 (10.3%) patients, presented with hypotension. Less frequent manifestations included melena, fatigue, fever, and vomiting, each reported in fewer than 5 cases. The mean time from polystyrene administration to the onset of symptoms was 5.5 d.

Comorbidities and laboratory values

Chronic kidney disease was reported in 37 (63.7%) patients, followed by hypertension (34.4%) and type 2 diabetes mellitus (20.6%). Strikingly, 75.8% of patients had some form of kidney disease, such as acute kidney injury, chronic kidney disease, end-stage renal disease, or had undergone kidney transplantation. The mean potassium levels prior to treatment initiation were 6.5 mmol/L.

Sites of inflammation and diagnostic procedures

The most commonly affected sites of inflammation were the cecum, rectum, and small intestine, accounting for 31%, 25.8%, and 22.4% of cases, respectively. Colonoscopy was mentioned in 28 (48.2%) of the reports, with biopsy being performed in 51 (87.9%) patients. Detailed findings from these diagnostic procedures are summarized in Table 2.

Treatment and outcomes

Out of the 59 patients, 29 (50%) required surgical intervention, with one patient necessitating reoperation. Among patients with available data, 39 (67.2%) experienced a favorable outcome, while 12 (20.6%) succumbed to the condition.

Table 1 Baseline features in 59 patients with colitis induced by polystyrene

Variable	Patients, <i>n</i> = 59 (100%)
Mean age (yr) (SD)	60.6 ± 16.6
Sex (male)	35 (60.3)
Signals and symptoms	
Abdominal pain	35 (60.3)
Bloating	18 (31)
Hematochezia	18 (31)
Constipation	7 (12)
Diarrhea	7 (12)
Hypotension	6 (10.3)
Melena	4 (6.9)
Fatigue	4 (6.9)
Fever	4 (6.9)
Vomiting	4 (6.9)
Pneumoperitoneum	3 (5.1)
Gastrointestinal involvement	
Cecum	18 (31)
Rectum	15 (25.8)
Small intestine	13 (22.4)
Transverse colon	10 (17.2)
Ascendent colon	9 (15.5)
Sigmoid	9 (15.5)
Descendent colon	8 (13.7)
Pancolitis	3 (5.1)
Stomach	2 (3.4)
Mean potassium levels (mmol/L) (SD)	6.5 ± 0.98
Comorbidities	
Chronic kidney disease	37 (63.7)
Hypertension	20 (34.4)
Type 2 diabetes	12 (20.6)
Peripheral arterial disease	7 (12)
Coronary artery disease	6 (10.3)
Polystyrene type	
Calcium (Kalimate)	11 (18.9)
Sodium (Kayexalte)	47 (81)
Mean polystyrene dose (g) (SD)	83.6 ± 70
Administration route	
Per os	38 (65.5)
Retal	5 (8.6)
Per os and retal	3 (5.1)
Mean time of onset symptoms (d) (SD)	5.5 ± 6.9
Biopsy	51 (87.9)

Treatment	
Surgery	29 (50)
Outcomes	
Recovery	39 (67.2)
Death	12 (20.6)
Mean time to outcome (d) (SD)	36.7 ± 35.5

The mean time to symptom resolution was 36.7 d, ranging from 1 to 120 d.

Quality assessment

In the quality assessment of the included cases, 2 (3.3%) were classified as having low quality, while the remaining 57 (96.7%) were considered to have moderate quality. None of the cases were categorized as high quality.

DISCUSSION

This systematic review delves into the analysis of documented cases of SPS-induced colitis, shedding light on the importance of collecting data on medication-related adverse events to enhance healthcare safety. Hyperkalemia, if left untreated, poses significant threats such as severe arrhythmias, cardiac arrest, and fatality[11]. The use of SPS for managing hyperkalemia has a historical legacy dating back to the 1960s[12], even though robust evidence substantiating its safety and efficacy remains scant[2].

Notably, mild adverse effects associated with SPS include symptoms like diarrhea, constipation, abdominal pain, bloating, nausea, and vomiting[13]. In the systematic review, bloating was reported in 31% of cases as a minor adverse effect, while vomiting occurred in 7% of patients. However, it is crucial to distinguish these relatively well-tolerated mild effects from severe adverse outcomes potentially linked to SPS use, which can significantly increase morbidity and mortality[14]. Such severe outcomes encompass colitis, ischemic colonic necrosis, seizures, confusion, irregular heartbeat, and pneumoperitoneum[13]. This systematic review reveals that all the cases included presented with colitis, and some cases developed more severe consequences.

Interestingly, descriptions of intestinal lesions first emerged in 1987 when catastrophic colonic necrosis was documented in five cases[15,16]. Subsequently, in 2012, a cohort study involving 2194 inpatients identified colonic necrosis in 82 cases related to SPS use[17]. Studies have reported varying incidences of colon necrosis after drug administration, ranging from 0.14% to 1.8%, with a higher incidence observed in the postoperative period[5,18]. Additionally, other concerning findings associated with SPS use, such as the three cases of pneumoperitoneum requiring urgent laparotomy, have been reported[19,20]. The characteristics of the patients are detailed in Tables 1 and 2.

Although these cases, though less common, are often detected early due to patients' complaints of increased abdominal pain and distention[5]. Typically, the time to the initial manifestation is around two days. A retrospective cohort study involving 19530 adults found that new users and users receiving the recommended dose 'per label' had a higher risk of adverse effects compared to chronic users and those on lower doses[21,22]. After adjusting for 26 covariates, SPS use was associated with hospitalization or death due to intestinal ischemia/thrombosis or gastrointestinal ulcers and perforation (HR 1.25, 95%CI 1.05-1.49)[21,22]. Therefore, the threshold dose for deleterious effects has yet to be determined, and caution is advised when prescribing this medication, especially for more fragile patients[4].

In a prior systematic review, 91% of included cases had a history of renal disease, a proportion slightly higher than the 75.8% observed in this study[4]. This aligns with expectations, as SPS is commonly used in patients with renal conditions. Other common comorbidities identified in our work included hypertension and diabetes mellitus, both of which are associated with chronic kidney disease[8,23,24]. In the literature, potential risk factors associated with deleterious adverse effects include uremia, hypovolemia, peripheral vascular disease, and immunosuppressive therapy, all of which were also evident in the cases reviewed[18,25-28].

Typically, the colon is the gastrointestinal segment most frequently affected by SPS-induced complications. These lesions necessitate endoscopic/colonoscopy analysis with biopsy to rule out differential diagnoses, such as cancer[16]. Gastric involvement is less common and was identified in only two cases in our review[29,30]. Biopsy results typically reveal intestinal necrosis, ulcers, or perforations, with an accumulation of SPS crystals in more than 90% of tissue samples[5]. The presence of kayexalate crystals in pathology specimens differentiates kayexalate-induced necrosis from ischemic necrosis[5]. Histologic evidence of angulated crystals of sodium polystyrene sulfate in areas of mucosal erosions, ulcerations, or frank necrosis strongly suggests the diagnosis[31]. Other associated findings include inflammatory exudates, pseudomembrane formation, and acute/chronic serositis[32]. These crystals are typically identified adhered to the mucosa or embedded within the inflammatory milieu and ulcerations[5]. Thus, to arrive at a definitive diagnosis, it is imperative to rule out conditions that can mimic SPS-induced effects, such as neoplasms, inflammatory diseases, and infectious diseases[16]. These histological characteristics are summarized in Table 2.

However, the pathophysiological mechanism underlying these lesions remains incompletely understood[4]. One of the most widely accepted theories suggests that the presence of renin in high concentrations among patients with renal failure plays a pivotal role. Activation of renin and subsequent splanchnic vasoconstriction can lead to non-occlusive

Table 2 Summary of systematically reviewed clinical cases

Ref.	Country	Age (yr)	Sex	Polystyrene type	Total dose (g)	First symptom (d)	Symptoms	Gastrointestinal compromise	Colonoscopy	Histology	Outcomes
Patel <i>et al</i> [52], 2017	United States	45	M	Kayexalate	30	-	None	Small intestine, cecum, ascending colon, transverse colon	Large ulcers at terminal ileum hepatic flexure and rectum	Small bowel: Acute enteritis and basophilic crystals with "fish-scales"	Recovery
Mizukami <i>et al</i> [53], 2016	Japan	64	M	Kayexalate	NR	30	Hematochezia	Rectum	Multiple ulcers were found in the upper to mid-rectum	Rectum: SPS crystals	Recovery
Rogers <i>et al</i> [33], 2001	United States	55	M	Kayexalate	NR	5	Diarrhea, Melena, Abdominal Pain	Sigmoid colon, descending colon	Large rectal ulcer and surrounding edematous and boggy mucosa	Rectum: Acute transmural necrosis with inflammatory and necrotic debris on the surface. Crystalloid foreign materials that were adherent to the ulcer bed	Recovery
Cervoni <i>et al</i> [54], 2015	United States	58	M	Kayexalate	NR	21	None	Descending colon	Severely friable mucosa with ischemic-appearing ulceration and apparent site of perforation in the proximal descending colon	Descending colon: Basophilic crystals with a mosaic pattern resembling fish scales	Recovery
Singla <i>et al</i> [55], 2016	United States	50	F	Kalimate	15	2	Constipation, Abdominal Pain, Bowel Sounds Were Absent	Cecum	NR	Cecum: Colonic necrosis and presence of SPS crystals in necrotic colonic mucosa	Recovery
Buraphat <i>et al</i> [34], 2019	Thailand	61	M	Kayexalate	210	NR	Constipation, Abdominal Pain	Small intestine	NR	Small intestine: Multiple erosions with ischemic changes and basophilic angulated crystals on the surface, Sigmoid Colon: numerous basophilic angulated crystals with a fish scale appearance were observed adhering to the surface of the mucosa	Death
Buraphat <i>et al</i> [34], 2019	Thailand	74	F	Kayexalate	150	NR	Abdominal Pain	Cecum	NR	NR	Death
Buraphat <i>et al</i> [34], 2019	Thailand	89	F	Kayexalate	180	NR	Constipation, Abdominal Pain	Sigmoid colon	NR	NR	Recovery
Fiel <i>et al</i> [19], 2018	Brazil	56	M	Kayexalate	NR	7	Constipation, Abdominal Pain, Fatigue, Abdominal Distension, Pneumoperitoneum, Hypokalemia CPS Bezoar	Cecum	NR	Serositis and transmural ischemia	Death
Jacob <i>et al</i> [1], 2016	India	75	M	Kalimate	NR	7	Abdominal Pain	Sigmoid colon	Inflamed edematous and ulcerated cecum, small ulcer with slough 4–5 cm from anal verge rectum, Stricture in splenic flexure scope could not be passed beyond, nodularity with superficial ulceration in rectum, ulcers	All biopsies showed similar findings with ulceration and inflammatory granulation tissue in most. Crystals which were basophilic and irregular ranging from 1 to 200 in number, ranging in size from 50 to 150 μ were noted. They had a mosaic or	Recovery

									in rectum and sigmoid colon	ribbed pattern or both	
Jacob <i>et al</i> [1], 2016	India	72	M	Kayexalate	NR	7	Abdominal Pain	Rectum	NR	Equal above	Recovery
Jacob <i>et al</i> [1], 2016	India	72	M	Kayexalate	NR	7	Abdominal Pain	Rectum	NR	Equal above	Recovery
Jacob <i>et al</i> [1], 2016	India	64	F	Kayexalate	NR	7	NR	Descending colon	NR	Equal above	Recovery
Jacob <i>et al</i> [1], 2016	India	48	F	Kayexalate	NR	7	NR	Rectum	NR	Equal above	Death
Jacob <i>et al</i> [1], 2016	India	52	M	Kayexalate	NR	7	NR	Sigmoid, Rectum	NR	Equal above	Death
Joo <i>et al</i> [8], 2009	South Korea	34	F	Kayexalate	215	2	Hematochezia	Descending colon	Diffuse active ulceration with mucosal necrosis and hemorrhage from the rectum to beyond the reach of an endoscope	Colitis with mucosal necrosis or ulceration and irregular shaped and sized angulated crystals with a characteristic crystalline mosaic pattern on the mucosa and ulcer bed tissue and within the necroinflammatory debris	Death
Akagun <i>et al</i> [56], 2011	Turkey	78	F	Kayexalate	60	2	Abdominal Pain, Pneumoperitoneum	Sigmoid colon	NR	Necroinflammatory debris and various sized fragments of basophilic crystalloid material with angulated margins on microscopic examination	Recovery
Cheng <i>et al</i> [20], 2021	Australia	53	F	Kayexalate	30	15	Diarrhea, Vomiting, Abdominal Pain, Abdominal Distension, Fever, Pneumoperitoneum	Transverse colon	NR	Multiple discrete areas of deep ulceration with intramural necrosis abscess formation and focal transmural penetration SPS crystals were present in the inflammatory debris	Death
Castillo-Cejas <i>et al</i> [57], 2014	Spain	73	M	Kayexalate	NR	NR	Hypotension	Cecum, ascending colon, transverse colon	Ischemic lesions in cecum, ascending colon and hepatic angle	Ascending colon: Mucosal necrosis and Kalimate crystals with their characteristic mosaic pattern within the granulation tissue from one of the colonic ulcers	Recovery
Thomas <i>et al</i> [23], 2009	United States	64	F	Kayexalate	90	27	Hematochezia, Abdominal Pain, Abdominal Distension, Hypotension	Sigmoid colon, Rectum	Friable area of 15 to 25 cm from the anal verge	Rectum: Ulcerated mucosa and prominent granulation tissue with small eosinophilic angulated crystals embedded in mucosal ulcers	Recovery
Bomback <i>et al</i> [31], 2009	United States	56	F	Kayexalate	15	NR	Abdominal Pain	Transverse colon	Large sessile mass in the midtransverse colon	Transverse colon: Crypt miniaturization with leakage of red blood cells and fibrin into the lamina propria associated with polygonal basophilic crystals	Recovery
Scott <i>et al</i> [37], 1993	United States	48	M	Kayexalate	50	0.5	Abdominal Pain, Abdominal Distension	Descending colon, Sigmoid colon, Rectum	The rectum, sigmoid, and left colonic mucosa were erythematous and friable. The mucosa became frankly necrotic at the splenic flexure	NR	Recovery

Chou <i>et al</i> [58], 2011	Taiwan	30	M	Kayexalate	90	3	Hematochezia	Transverse colon	Colon ulcers included scattered erosion longitudinal ulcerations and sharply defined segment of involvement	Transverse colon and splenic flexure: Necrotic debris adjacent to eroded colonic mucosa. A few basophilic and rhomboid crystals with fish-scale-like mosaic pattern were identified	Recovery
Ribeiro <i>et al</i> [59], 2017	Portugal	72	M	Kalimate	NR	1	Abdominal Pain	Cecum, ascending colon	Congestive and ulcerated mucosa in the right colon and a deep necrotic ulcer in the cecum, with a diameter of 40 mm	Cecum: Necroinflammatory and granulation tissue containing basophilic-stained polystyrene sulfonate crystals	Recovery
Wootton <i>et al</i> [60], 1989	United States	48	M	Keyexalate	200	0.5	Abdominal Pain, Abdominal Distension, Fever	Transverse colon	NR	Transverse colon: Patchy transmural infarction of the colon. Near the necrotic mucosa were large quantities of amorphous Kayexalate material	Recovery
Chelcun <i>et al</i> [61], 2012	United States	51	M	Keyexalate	30	NR	Melena	Small intestine	Large ulcer surrounded by erythema was found at the ileocecal valve	Ileocecal valve: Reactive colonic mucosa with ulceration and prominent acute inflammatory exudate containing basophilic crystals consistent with SPS use	Recovery
Tapia <i>et al</i> [62], 2009	Switzerland	71	F	Kayexalate	80	10	Diarrhea, Abdominal Pain, Vomiting	Cecum, ascending colon	Segmental, circumscribed colitis in the cecum and at the left flexure	Cecum and left flexure: Segmental ulcers lightly distorted crypts with mucus depletion and fibrosis in the lamina propria accompanied by a mixed inflammatory infiltrate with lymphocytes and some neutrophils. Colon fragments with the angular crystals/foreign bodies	Recovery
Trottier <i>et al</i> [63], 2009	Canada	24	M	Kayexalate	110	1	Constipation, Abdominal Pain, Abdominal Distension, Fever, Hypotension	Small intestine	NR	Ileum-multifocal, acute ulceration. Patchy transmural necrosis and SPS crystal deposition within the intestinal mucosa	Recovery
Kao <i>et al</i> [64], 2015	Taiwan	59	M	Kalimate	120	2	Abdominal Pain, Abdominal Distension, Hypotension	Small intestine, Sigmoid colon	NR	Ileum-transmural necrosis and perforation with basophilic angulated crystals extending from the ulcerated luminal surface into the transmural	Death
Singhania <i>et al</i> [25], 2020	United States	30	M	Kayexalate	15	0.16	Hematochezia, Vomiting, Abdominal Pain, Abdominal Distension	All colon	NR	NR	NR
Goutorbe <i>et al</i> [65], 2011	United States	73	M	Kalimate	15	3	Abdominal Pain, Hypotension, Tachycardia	Small intestine, cecum	NR	Transmural abscess massive inflammatory infiltrate, ulceration and inflammation of the ceca mucosa with a fibrinous and purulent coating. Small frayed-purple or blue angulated crystals	Death
Gerstman <i>et al</i> [18], 1992	United States	43	NR	Kayexalate	50	2	Abdominal Pain, Abdominal Distension, Confusion, Blood in the Gastric Aspirate	Cecum	NR	NR	Recovery
Gerstman <i>et al</i>	United	42	NR	Kayexalate	135	NR	Hematochezia, Abdominal	Cecum	NR	NR	Recovery

<i>al</i> [18], 1992	States						Pain					
Aguilera <i>et al</i> [66], 2000	Spain	83	M	Kayexalate	NR	1	Abdominal Pain, Hypotension	Small intestine	NR		Transmural necrosis and in its course and in the peritoneal surface there are numerous basophilic crystals with hematoxylin	Death
Gardiner <i>et al</i> [30], 1997	Canada	66	M	Kayexalate	240	NR	NR	Stomach, small intestine	NR		Coagulative necrosis of the mucosa with overlying purple rhomboid kayexalate crystals, submucosal edema and acute transmural inflammation	Death
Gardiner <i>et al</i> [30], 1997	Canada	71	F	Kayexalate	105	NR	Hematochezia	Small intestine, ascending colon	NR		Hemorrhagic mucosal necrosis associated	Death
Pusztaszeri <i>et al</i> [67], 2007	France	87	M	Kalimate	NR	NR	Abdominal Distension	Small intestine	NR		Kayexalate crystals, submucosal edema and acute transmural inflammation	NR
Islam <i>et al</i> [26], 2015	United States	71	F	Kayexalate	15	0.5	Vomiting, Abdominal Pain, Nausea	Cecum	NR		Diffuse mucosal necrosis with dark purple crystals	Recovery
Kardashian <i>et al</i> [68], 2016	United States	65	F	Kayexalate	NR	2	Hematochezia, Constipation, Abdominal Pain, Fatigue, Abdominal Distension	NR	NR		Dark purple SPS crystals	Recovery
Shahid <i>et al</i> [69], 2019	United States	78	F	Kayexalate	43	1	Abdominal Pain	Cecum, ascending colon	NR		Findings of ischemic colitis with detached purple refractile material	Recovery
Strader <i>et al</i> [70], 2017	United States	60	M	Kayexalate	NR	NR	Nr	Cecum	4cm circumferential, ulcerating mass in the cecum partially obstructing the lumen as well		Biopsies in both areas reveal material morphologically consistent with kayexalate with associated colitis, ulceration and necroinflammatory debris, with no evidence of malignancy	Recovery
Albeldawi <i>et al</i> [71], 2014	United States	61	M	Kayexalate	NR	NR	Hematochezia, Fatigue, Dizziness	Cecum	Evidence of colitis and localized ulcerations in the cecum		Revealed basophilic, non-polarizable, rhomboid-like crystals without evidence of necrosis	NR
Ofori <i>et al</i> [72], 2017	United States	80	F	Kayexalate	NR	7	Hematochezia, Abdominal Pain, Abdominal Distension	Transverse colon	Revealed lumen obstructing clot in the mid transverse colon with adjacent unhealthy mucosa which was bleeding upon contact. Scope could not be advanced safely past the large clot		NR	Recovery
Abramowitz <i>et al</i> [27], 2014	United States	70	F	Kayexalate	NR	NR	Hematochezia	Rectum	Scattered diverticula throughout the colon and a 2 cm × 3 cm semi-circumferential friable rectal ulceration just proximal to the anorectal junction with active oozing of blood		Fragments of granulation tissue and crystalline fragments consistent with Kayexalate that were seen on the surface	NR
Rugolotto <i>et al</i> [73], 2007	Italy	0,01	NR	Kayexalate	6.8	4	Abdominal Distension	Small intestine	NR		Ileum specimen showed multiple areas of trans-mural necrosis, whereas the lumen	Recovery

										showed basophilic and Zihel–Neelsen stain positive angulated crystals surrounded by fibrinoid and giant cells exudates	
Edhi <i>et al</i> [74], 2018	United States	73	M	Kayexalate	30	1	Abdominal Distension	Cecum, ascending colon, transverse colon, descending colon	Highly consistent with ischemic colitis in the descending colon	Inflamed and ulcerated colonic mucosa and basophilic, non-polarizable, angulated, intramucosal crystals, highly consistent with SPS induced ischemic colitis	Recovery
Chatelain <i>et al</i> [75], 2007	France	46	M	Kayexalate	150	NR	Diarrhea, Hematochezia	Descending colon, Sigmoid colon, Rectum	Segmental ulcerations of the sigmoid colon	Ischemic colitis with ulcerations and transmural inflammation. Kayexalate crystals were present in the colonic lumen, adherent to ulcers. Thickened and fibrous submucosa containing numerous basophilic and purple polygonal crystals surrounded by macrophages and giant cells	Recovery
Oliveira <i>et al</i> [7], 2018	Portugal	83	F	Kayexalate	NR	2	Diarrhea, Abdominal Pain	Rectum	Visualization of the rectum, a depressed area in the lower rectum, partially ulcerated, without apparent necrosis was found and biopsied	Presence of basophilic structures with mosaic pattern, lilar to fish scales, surrounded by an intense active chronic inflammatory infiltrate, aspects compatible with lesion caused by ion exchange resin deposition (Kayexalate Crystals)	Recovery
Florian <i>et al</i> [76], 2019	United States	69	M	Kayexalate	NR	NR	Hematochezia	Cecum, Ascending colon	Extensive circumferential ulceration and pseudomembrane in the cecum and proximal ascending colon. Persistent ulcerations with erythematous friability in the same area	Revealed acute reactive epithelial atypia with embedded polystyrene sulfonate crystals	NR
Lee <i>et al</i> [77], 2017	United States	66	F	Kayexalate	NR	5	Hematochezia	Rectum	Two relatively isolated ulcers located in the transverse colon and in the rectum	The rectal ulcer demonstrated findings of crystal-like structures suggestive of kayexalate crystals	Recovery
Chang <i>et al</i> [78], 2020	United States	66	M	Kayexalate	30	NR	NR	Small intestine	NR	Acute ischemic enteritis featuring mucosal ulceration associated with crystals morphologically compatible with SPS, submucosal arterial and venous thrombosis and acute organizing serositis	Recovery
Moole <i>et al</i> [79], 2014	United States	80	F	Kayexalate	30	1	Diarrhea, Hematochezia, Abdominal Pain, Abdominal Distension	Sigmoid colon, Rectum	Severe well demarcated colitis in the rectosigmoid junction with a large amount of blood clots at the demarcation	Showed distal rectosigmoid ischemic colitis, with mucosal and focal submucosal necrosis and crystals consistent with Kayexalate	Recovery
Edhi <i>et al</i> [24], 2017	United States	78	M	Kayexalate	NR	NR	NR	Transverse colon, Descending colon	Diffuse moderate inflammation in the descending colon, with severe inflammation in the transverse colon	Ulceration of the colonic mucosa with basophilic crystal consistent with SPS induced injury and no features of ischemia, infectious changes or granulomas	NR
Huang <i>et al</i> [80], 2011	United States	57	M	Kayexalate	160	5	Constipation, Abdominal Pain, Abdominal Distension	NR	NR	Demonstrated crystals characteristic of SPS toxicity and concluded that the patient's	Recovery

Gürtler <i>et al</i> [81], 2018	Switzerland	56	M	Kayexalate	NR	1	Melena, Abdominal Pain	Small intestine	Gastroscopy demonstrated severe ulcerative duodenitis with no evidence of active bleeding	bowel perforation was likely caused by SPS Revealed a severe erosive duodenitis. Abundant SPS crystals were detectable within the fibrinoleukocytic exudates of the duodenal ulcers and on the surface of the inconspicuous gastric mucosa	Recovery
Hajjar <i>et al</i> [29], 2018	Canada	48	M	Kayexalate	NR	NR	Abdominal Pain, Abdominal Distension	Stomach	NR	Revealed the presence of fibrinoleukocytic debris with rhomboid, birefringent crystals, suggestive of Kayexalate in the gastric wall	Recovery
Almulhim <i>et al</i> [28], 2018	Saudi Arabia	64	M	Kayexalate	30	9	Hematochezia, Melena, Abdominal Pain, Fatigue, Fever, Anemia	Descending colon, transverse colon	Findings were suggestive of right colon colitis with possible etiology of ischemia and necrotic appearing mucosa	Specimen was found to be granulated and contain SPS crystals	Recovery
Dunlap <i>et al</i> [5], 2016	United States	55	F	Kayexalate	30	2	Diarrhea, Hematochezia, Abdominal Pain, Abdominal Distension, Peritonite	All colon	Flexible sigmoidoscopy, which identified several ulcerations that were biopsied, later revealing ischemic necrosis of the bowel	Diffusely hemorrhagic with extensive multifocal ulcerations. Crystalloid particles consistent with kayexalate were identified throughout the bowel wall	Recovery
dos Santos <i>et al</i> [12], 2021	Brazil	77	F	Kayexalate	120	4	Diarrhea	Sigmoid colon	Revealed edema, enanthema, and erosion into the sigmoid colon	Typical fish scale-like SPS crystal	Recovery

NR: not reported; SPS: Sodium polystyrene sulfonate.

mesenteric ischemia, predisposing the colonic mucosa to injuries and electrolyte disturbances[32,33]. Nevertheless, it remains unclear why patients with renal failure are more susceptible to this catastrophic complication. It may simply be attributed to their higher likelihood of being hyperkalemic, necessitating treatment with higher doses of SPS than other patients[33].

Alternative theories propose that polystyrene's high water affinity leads to bulk formation with shear-thickening flow behavior, resulting in clumping and resin clogging, particularly in patients with compromised gastrointestinal motility [34]. This leads to resin impaction, subsequent gut obstruction, ischemic necrosis, and perforation, analogous to findings in stercoral colonic perforation[35]. Details about the drug are available in Table 3.

Despite the relatively common use of SPS, there is limited evidence regarding its effectiveness and safety in the literature. Therefore, vigilance is warranted regarding the drug's adverse effects[36]. A previous systematic review published in 2013 reported serious adverse reactions associated with colonic necrosis, which occupied a prominent position and resulted in a mortality rate of 33% among affected patients, higher than the 21% mortality rate observed in our study[4]. Conversely, in a double-blind, randomized, placebo-controlled trial, colonic necrosis was not reported[3]. However, the trial involved only 31 participants who were followed for a short period (7 d) and were less ill than the general patients who typically receive the medication[32]. Therefore, prescribing SPS should be a carefully considered decision, taking into account each patient's specific circumstances, especially in cases of sicker patients, such as older individuals and those with gastrointestinal hypomotility. Higher mortality rates have been observed in colitis induced by SPS. Therefore, it is essential to consider alternative approaches for controlling hyperkalemia. If alternative options are not available, it is strongly advised to implement routine monitoring to enable early detection of potential complications

Table 3 Sodium polystyrene sulfonate characteristics – adapted from Rahman *et al*[13]

Indications	Mechanism of action	Administration	Dose (g)	Adverse effects (mild)	Adverse effects (serious)	Contraindications
Hyperkalemia	Resin exchanges sodium with potassium ions from the intestinal cells	Orally or rectally	Usually, 15 to 60 daily	Diarrhea, nausea, vomiting, loss of appetite, bloating	Ischemic colonic necrosis, constipation, seizures, confusion, abdominal pain, irregular heart beat	Hypokalemia, previous hypersensitivity to SPS, bowel obstruction, neonates with reduced gut motility

SPS: Sodium polystyrene sulfonate.

[19,36].

In the adapted quality assessment tool, the majority of cases were classified as having moderate quality (96.6%)[10]. None of the cases were categorized as high quality. This was primarily due to causality questions, which, for example, implicate the danger of reexposing the patient to SPS. Additionally, none of the cases met the criteria to score in question one, as the authors did not specify whether the cases were unique in their centers. Nonetheless, only two cases were classified as low quality[34,37]. Further details can be found in [Supplementary material](#).

The primary limitations of our study were the limited number of available cases ($n = 59$) and the scarcity of data in many of the reviewed cases. Despite our efforts, some full articles could not be located, even after contacting the authors, which could be attributed to the publication year. The inclusion of articles was restricted to those published in English, Spanish, French, or Portuguese, potentially resulting in the omission of articles in other languages. Despite these limitations, most of the variables presented in Tables 1 and 2 provide valuable insights into the characteristics of the patients.

Considering that observational trials suggest that SPS may lower serum potassium levels, but not without the risk of bowel injury[2] and death resulting from hyperkalemia is an unacceptable outcome[38], alternative options for addressing elevated potassium levels should be explored, and SPS should be considered a drug of last resort[39]. Some authors argue that despite many decades of experience with SPS and its low cost, it would be premature to abandon it in favor of more expensive alternatives with similar side effects or undefined long-term toxicity[17]. When evaluating patients exposed to SPS with diarrhea, it is essential to always consider a broad range of potential differential diagnoses for colitis and diarrhea in this group of patients, such as inflammatory bowel disease[40–42], infectious enteritis and colitis [43–45], angiotensin II receptor blocker induced sprue-like enteropathy[46], celiac disease[47,48], foreign body ingestion or food poisoning[49], neoplasm[50] or pellagra[51].

CONCLUSION

In conclusion, alternative methods such as hemodialysis or glucose, insulin, or bicarbonate injections may be more effective in controlling hyperkalemia[18]. There is currently insufficient high-quality data to estimate the number of adverse events associated with SPS use, making it challenging to determine whether the benefits outweigh the risks[2, 38]. Moreover, it is crucial to acknowledge that the mortality rate was notably significant, standing at 20.6% in this review. Therefore, future studies should ideally involve randomized controlled trials with an adequate number of patients to investigate the real risks and benefits of this drug.

ARTICLE HIGHLIGHTS

Research background

The study details the significance of Sodium Polystyrene Sulfonate (SPS) in managing hyperkalemia, a life-threatening condition. SPS, used to remove excess potassium, has side effects, including severe gastrointestinal complications. The exact mechanism of SPS-induced colitis is unclear, but it primarily affects the colon, requiring biopsy for diagnosis.

Research motivation

Comprehensive understanding of the SPS therapy and colitis relationship is crucial for patient safety. This research addresses knowledge gaps, aiming to contribute to future studies in drug safety and gastroenterology.

Research objectives

This study's main goal is to systematically review cases of SPS-induced colitis to understand its prognosis and influencing factors. Achieving these objectives enhances awareness of risks tied to SPS therapy, aiding clinical decisions for hyperkalemia management and guiding future research on risk mitigation.

Research methods

This systematic review followed the PRISMA guidelines for transparency and methodological rigor. A comprehensive search strategy covered multiple databases and utilized manual searches. Inclusion criteria prioritized case reports or case series studies, with language inclusion restricted to English, Spanish, French, or Portuguese. A two-step screening process and data extraction by independent reviewers ensured rigorous analysis. Methodological quality assessment employed a modified tool, addressing specific aspects related to polystyrene-induced colitis. Data were analyzed using descriptive statistics, providing a comprehensive dataset characterization.

Research results

The review examined 442 references, including 51 which comprised 59 cases meeting the criteria. The majority of cases were from the United States (48.2%). The patients age varied from less than 1 year to 89 years and were predominantly diagnosed with SPS-induced colitis. Common symptoms included abdominal pain, bloating, and gastrointestinal issues, with chronic kidney disease being prevalent. Diagnostic procedures such as colonoscopy and biopsies were frequently conducted. Surgical intervention was necessary for 50% of patients, and most had favorable outcomes, with a mean time to symptom resolution of 36.7 days.

Research conclusions

This systematic review underscores the importance of monitoring adverse events related to SPS in hyperkalemia treatment. It differentiates mild from severe side effects, advocating for alternative hyperkalemia management, especially for older or fragile patients due to higher associated mortality. The exact mechanisms remain unclear, but factors such as renin concentration and water affinity are implicated.

Research perspectives

Future research should prioritize randomized controlled trials to assess SPS use, considering its effectiveness and risks. Alternative hyperkalemia management methods and cautious SPS prescription are crucial, with a focus on addressing knowledge gaps for informed clinical decisions.

FOOTNOTES

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