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Original article

# Histopathological lesions of the gastrointestinal tract associated with the use of polystyrene sulfonate and sevelamer: a meta-analysis

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**Summary**

**Background.** Gastrointestinal severe adverse events such as ulceration and perforation have been reported for sodium or calcium polystyrene sulfonate and sevelamer. However, their role in the pathogenesis is unclear. Chronic kidney disease is a well known risk factor, while the role of hypertension and/or diabetes is uncertain.

**Methods.** A meta-analysis of the published literature was conducted to review the clinical features, risk factors and histopathological findings of patients who experienced gastrointestinal adverse events after administration of polystyrene sulfonate or sevelamer.

**Results.** The meta-analysis indicated that patients were more likely to show necrosis and/or perforation when the resin used was polystyrene sulfonate compared to sevelamer ($p < 0.001$). Death was more likely in patients taking polystyrene sulfonate compared to sevelamer ($p < 0.001$).

**Discussion.** The results show that sevelamer is more likely to lead to inflammation or ulceration in the gastrointestinal tract than polystyrene sulfonate, which is more likely to be associated with severe gastrointestinal adverse events such as necrosis and/or perforation. Polystyrene sulfonate is significantly associated with death compared to sevelamer.

**Key words:** polystyrene sulfonate, sevelamer, gastrointestinal adverse events

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## Background

Medication resins are orally ingested drugs that allow ion exchange. They are not absorbed but can crystallize in the gastrointestinal tract and lead to concretions, which can be seen under a light microscope. The most common ones are sodium or calcium polystyrene sulfonate and sevelamer [1-3]. Side effects are usually mild, although severe adverse events have been reported [4].

Sodium polystyrene sulfonate (SPS) had been administered with 70% sorbitol until some patients experienced intestinal necrosis [5]. The experiment of Lillemoe et al. on rats seemed to demonstrate that sorbitol, and not SPS alone, was responsible for colonic necrosis because no rat treated with SPS alone developed this complication and all cases were seen in rats that received a preparation of SPS and sorbitol or sorbitol alone. However, this finding has been questioned by a recent experiment. Ayoub et al. have shown that 33% sorbitol does not cause colonic necrosis in rats; they have also noticed a higher risk of necrosis in animals treated with SPS [6]. A similar adverse event has been report-

ed with calcium polystyrene sulfonate (CPS) [7]. Two systematic reviews of gastrointestinal adverse events have concluded that crystals are not only indicative of polystyrene sulfonate use, but also suggestive of direct damage to the gastrointestinal mucosa [5,8].

Sevelamer-related adverse events include intestinal ulceration and perforation [9,10]. A recent review of cases has concluded that their presence in injured mucosa is not sufficient to prove their direct role in the pathogenesis of the lesions. Indeed, some specimens show no pathological features except for sevelamer crystals. Larger studies are needed to clarify if this resin is truly pathogenetic or its presence is merely incidental [11].

The two systematic reviews on adverse events associated with the use of polystyrene sulfonate report that chronic kidney disease is a well known risk factor and stress the role of immunosuppression and postoperative state in the development of these side effects. Although hypertension and diabetes are common in these patients, not all authors consider them as risk factors [5,8]. On the contrary, diabetes is a supposed risk factor for the devolpoment of gastrointestinal adverse events in patients taking sevelamer [3].

Since there are few studies which focus on the histopathological alterations related to these drugs, we aim to review the clinical features, risk factors and histopathological findings of patients who experienced adverse gastrointestinal events after administration of polystyrene sulfonate or sevelamer.

## Materials and methods

PubMed, Web of Science and Scopus databases were searched for case reports and case series of gastrointestinal adverse events related to the administration of sodium or calcium polystyrene sulfonate and sevelamer hydrochloride or carbonate from 1973 to 2023. The search terms included "gastrointestinal", "polystyrene sulfonate" and "sevelamer". 1163 articles were found, which were reviewed at the title and abstract level with removal of duplicates. 104 full text articles were assessed for eligibility. They were included in this meta-analysis if the following information was provided: age, sex, administered drugs, outcome, symptoms, site of injury, histopathological findings, and comorbidities. Three were excluded because no histopathological specimens were examined. Another article was removed because clinical and histopathological information was not available. 100 articles were included in the present meta-analysis. Figure 1 shows the flow chart of the selection process.

The local Ethics Committee approved the present study (112/2023/TESS/UNIPR).

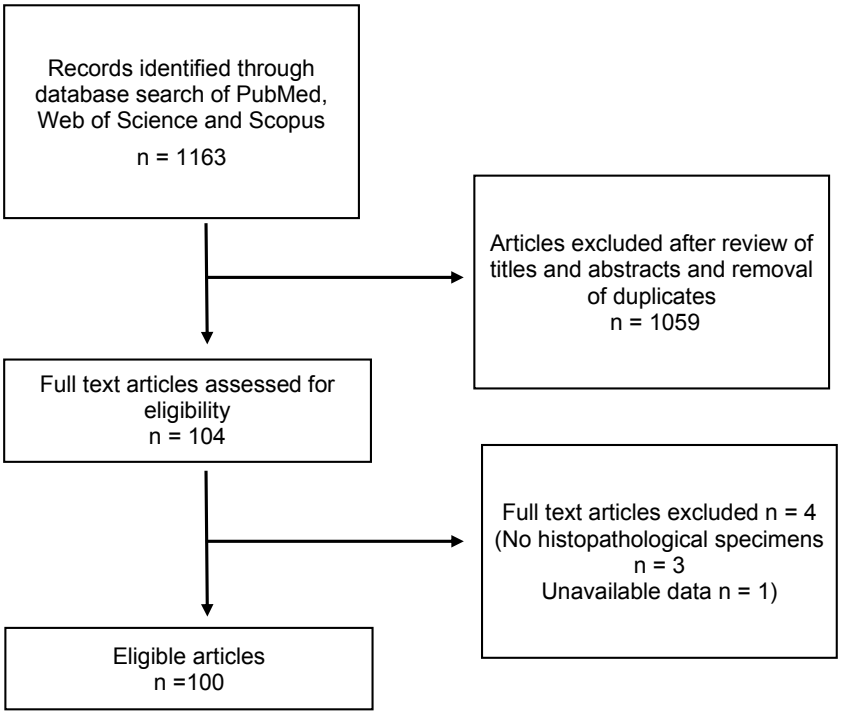


**Figure 1.** Flow chart of the selection process.

### Statistical analysis

The 100 articles were subjected to of statistical analysis. Categorical variables were expressed as absolute and relative frequencies. Continuous variables were reported as mean ± standard deviation. A chi-square test was used to compare categorical variables. A p-value less than 0.001 was considered statistically significant ($p < 0.001$).

## Results

Information on 130 studies was acquired from the 100 articles included in this study. Altogether, they described 237 cases of gastrointestinal adverse events following the administration of resins. The patients were found in 84 case reports, 14 case series and 2 systematic reviews.

Table I outlines the characteristics of the patients included in the meta-analysis.

Table II reports the clinical and histopathological features of adverse events as well as the patient outcome.

Table III compares the histopathological findings of patients taking the two resins. Patients were more likely to show necrosis and/or perforation when the resin used was polystyrene sulfonate as opposed to sevelamer ($p < 0.001$).

**Table I.** Patients characteristics.

| | |
|---|---|
| Sex: | |
| - Male | 138 (58.22%) |
| - Female | 99 (41.78%) |
| Mean age in years | 60±17 |
| Administered resins: | |
| - Sodium polystyrene sulfonate | 151 (63.71%) |
| - Calcium polystyrene sulfonate | 41 (17.30%) |
| - Sevelamer | 40 (16.88%) |
| - Sodium polystyrene sulfonate and sevelamer | 5 (2.11%) |
| Comorbidities: | |
| - Chronic kidney disease/end stage renal disease | 189 (79.75%) |
| - Hypertension | 83 (35.02%) |
| - Diabetes | 57 (24.05%) |
| - Atherosclerosis-related complications | 42 (17.72%) |
| - Previous transplantation | 16 (6.75%) |
| - Acute kidney injury | 12 (5.06%) |

**Table II.** Clinical and histopathological features of adverse events.

| | |
|---|---|
| Presenting symptoms: | |
| - Abdominal pain | 131 (55.27%) |
| - Gastrointestinal bleeding | 103 (43.46%) |
| - Nausea and/or vomiting | 27 (11.39%) |
| - Diarrhea | 23 (9.70%) |
| Affected organs: | |
| - Colon | 180 (75.95%) |
| - Small intestine | 35 (14.77%) |
| - Stomach | 21 (8.86%) |
| - Esophagus | 18 (7.59%) |
| - Rectum | 18 (7.59%) |
| - Duodenum | 10 (4.22%) |
| Main histopathological findings: | |
| - Ulceration | 138 (58.23%) |
| - Necrosis | 101 (42.62%) |
| - Perforation | 58 (24.47%) |
| - Inflammation only | 34 (14.35%) |
| - Crystals only | 4 (1.69%) |
| Outcome: | |
| - Alive | 155 (65.40%) |
| - Dead | 47 (19.83%) |
| - Not available | 35 (14.77%) |

**Table III.** Histopathological findings of patients taking the two resins.

| | Necrosis/ perforation | Ischemic injury/ inflammation |
|---|---|---|
| Polystyrene sulfonate | 113 | 84 |
| Sevelamer | 7 | 33 |

Table IV compares the outcome of patients taking the two resins. Death was more likely in patients taking polystyrene sulfonate compared to sevelamer ($p < 0.001$).

**Table IV.** Outcome of patients taking the two resins.

| | Alive | Dead |
|---|---|---|
| Polystyrene sulfonate | 127 | 47 |
| Sevelamer | 28 | 0 |

## Discussion

To the best of our knowledge, our meta-analysis of the literature on gastrointestinal adverse events associated with the use of resins is the largest on this topic and the only one which compares patients taking two different resins.

This work found that sodium polystyrene sulfonate led to more reports of serious side effects than calcium polystyrene sulfonate or sevelamer. There are two reasons which explain this finding. SPS is the oldest drug among the three and more commonly prescribed for hyperkaliemia than CPS, which is available worldwide but not in the United States [12,13]. As our results show, sevelamer is more likely to lead to inflammation or ulceration in the gastrointestinal tract than polystyrene sulfonate, which is more likely to be associated with severe gastrointestinal adverse events such as necrosis and/or perforation.

The most affected site was the colon followed by the small intestine. There were only 48 adverse events in the upper GI tract as compared to 226 in the lower GI tract. Since resins are not absorbed as they pass through the digestive system [1], this finding might be explained by higher transit time of the drugs in the distal digestive system in comparison to the proximal tract [14]. However, other factors might contribute to this predilection such as gastrointestinal dysmotility, which has been reported in patients with chronic kidney disease, and diverticular pouches, which are rare in the small intestine [15]. Both might lead to the deposition of crystals which increase the risk of mucosal damage in the colon [3,15-19].

Gastrointestinal bleeding was second only to abdominal pain as the presenting symptom and was due to ulceration, necrosis or perforation in the gastrointestinal tract. However, some patients who complained about bleeding only showed mucosal inflammation. These cases were seen among those who used sevelamer [20,21] .

Resins can also be incidental findings in the gastrointestinal tract: 4 patients showed the presence of crystals without significant histopathological changes: 3 cases were seen with sodium polystyrene sulfonate [22]; 1 case was seen with sevelamer [23]. They underwent endoscopy for abdominal pain, gastrointestinal bleeding or nausea and vomit. These were probably side effects of these drugs, however there were no signs of damage in the respective specimens. This suggests that crystals alone do not cause mucosal injury. As proven by a recent experimental study, gastrointestinal damage might be triggered by the disruption of the intestinal barrier, which is a consequence of diseases such as chronic kidney disease, hypertension and diabetes [24]. These were the most common medical conditions in the reviewed population.

Although we hypothesized that nephropathic patients who also had diabetes and/or hypertension were more likely to show necrosis or perforation, when we compared these subjects with nephropathic patients that did not have these risk factors, we found no significant differences in the likelihood of severe adverse events such as necrosis or perforation (data not shown). Therefore, we believe that chronic kidney disease alone can predispose to severe gastrointestinal adverse events in patients taking medication resins.

41 patients who used CPS all showed ulceration, necrosis and/or perforation similarly to the 151 patients who used SPS. Supposedly, the mechanism of gastrointestinal damage might be the same: it could be related to the fact that these resins form an insoluble matrix in the gastrointestinal tract that may ulcerate the mucosa in the presence of predisposing medical conditions [24].

Among patients with a gastrointestinal adverse event due to medication resins, we demonstrated that it was more common for those taking polystyrene sulfonate to show necrosis and/or perforation; in contrast, inflammation or ischemia were more likely in patients taking sevelamer. We also showed that polystyrene sulfonate was significantly associated with death compared to sevelamer. All patients who had taken sevelamer survived the event, whereas some patients did not after taking polystyrene sulfonate. In reality, there were three reports of death among patients who had taken sevelamer. However, they were unrelated to the use of the drug for two reasons: either there was a long time span between administration and death or the patients died due to other medical conditions [11,25,26]. On the contrary, some patients who had been administered polystyrene sulfonate experienced severe necrosis and/or perforation that ultimately led to death due to sepsis [22,27-38].

Our findings suggest that polystyrene sulfonate is more likely to lead to severe and probably fatal consequences than sevelamer. To the best of our knowledge, death has never been directly correlated to sevelamer, even though some patients experienced severe adverse events such as necrosis and/or perforation. On the contrary, polystyrene sulfonate was responsible for the death of some patients in the reviewed population due to severe gastrointestinal injury.

Our review of literature implies that the spectrum of gastrointestinal adverse events can be variable. Sometimes endoscopy is performed before surgery. This means that mucosal injury seen in endoscopic biopsies can progress to urgent surgery due to necrosis or perforation. Harel et al. reported that most dead patients showed necrosis in biopsies [5]. We hypothesize that the presence of necrosis in biopsies could be used to warn clinicians that the patient might risk urgent surgery, although this assumption needs to be confirmed in studies with both biopsy and resection specimen available.

Our meta-analysis has a few limitations: all information derives from case reports, case series and two systematic reviews; most studies are descriptions of one or few cases which provide heterogenous data that are supposedly comparable. Moreover, we cannot draw definitive conclusions on the prognostic value of necrosis due to the absence of studies with both biopsies and resection specimens.

In conclusion, polystyrene sulfonate and sevelamer may lead to similar gastrointestinal adverse events with different likelihood of severity. Although both may show necrosis and/or perforation, we have demonstrated that severe injury and death are more common in patients using polystyrene sulfonate. We suggest

that necrosis might be used in biopsies as a prognostic marker of severe gastrointestinal adverse events with possible resort to urgent surgery. However, larger studies and availability of both biopsies and resection specimens are needed to verify our hypothesis.

### Conflicts of interest statement

The authors declare that there is no conflict of interest regarding the publication of this article.

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### Authors' contribution

PC and GDR conceived the idea of this meta-analysis. MDS and EF gave the clinical perspective of this topic. GP made the statistical analysis. GDR wrote the manuscript. PC, GDR, NC and EC reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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