



REVIEW ARTICLE

Acute ischemic colitis associated with oral decongestant use: a systematic review

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Abstract

Background and Aim: Acute ischemic colitis (IC) has been linked with the use of oral decongestants. However, clinical evidence on this association remains limited. We aim to evaluate the occurrence and clinical outcomes of acute IC following over-the-counter (OTC) use of pseudoephedrine and phenylephrine.

Methods: We conducted a systematic review of the MEDLINE, Google Scholar, Scopus, and Embase databases between inception and July 20, 2022. Specific search terms were used. The inclusion criteria consisted of English-language articles describing acute IC secondary to pseudoephedrine or phenylephrine.

Results: A total of 18 case reports (level of clinical evidence: IV) fulfilled our inclusion criteria. The mean age of patients was 51.6 ± 15.3 years, with 14 (77.8%) cases reported in women. The clinical presentation was mainly related to abdominal pain 16 (88.9%), hematochezia 15 (83.3%), and/or abdominal tenderness 10 (55.6%). The medical background showed that 5 (27.8%) patients were previously healthy. In the 13 (72.2%) patients with comorbidities, hypertension 6 (46.2%), a history of tobacco use 5 (38.5%), and psychiatric illnesses 4 (30.8%) were commonly reported. Leukocytosis was encountered in 13 (72.2%) patients. Diagnostic investigations included a combination of computed tomography scan and colonoscopy in 10 (55.6%), colonoscopy alone in 6 (33.3%), and flexible sigmoidoscopy in 1 (5.6%) patient. Colonoscopic biopsy was the mainstay of diagnosis in 15 (83.3%) patients. Treatment was based on supportive care in 18 (100%), concurrent antibiotic use in 2 (11.1%), and surgical intervention in 1 (5.6%) patient. Recurrent episodes of IC occurred in 4 (22.2%) patients.

Conclusions: Acute IC secondary to oral decongestants remains a rare but important clinical phenomenon. Clinical suspicion and imaging findings are important for the early diagnosis.

Relevance to Patients: In unexplained cases of IC, clinicians should specifically inquire about oral decongestants since they are OTC and patients commonly fail to reveal their usage. These drugs should be avoided for transient cold symptoms, especially in women.

1. Introduction

Ischemic colitis (IC) is a well-known disease, with an annual incidence of 16 cases/100,000 person-years [1]. A prospective study conducted in 24 Spanish hospitals showed that IC was responsible for 1.28/1000 hospital admissions [2]. Colonic ischemia is predominantly caused by sudden reduction in blood flow, especially in watershed areas of the splenic flexure (Griffith's point) and rectosigmoid junction (Sudek's point), which leads to ischemic

injury [3]. The underlying pathophysiology of IC stems from the colonic susceptibility to hypoperfusion in such watershed areas. It frequently affects the elderly individuals as a sequel to vascular comorbidities [3]. Among vascular disorders, non-occlusive causes are predominant (>95% of cases) compared to occlusive causes [3]. The clinical, colonoscopy, and biopsy findings are important for its detection [4]. However, the diagnosis and treatment of IC often present diagnostic and therapeutic conundrums [4]. A wide variety of etiologies have been reported to precipitate colonic ischemia. The conditions leading to mesenteric venous thrombosis, small vessel disease, hemodynamic compromise, mechanical colonic obstruction, blood dyscrasia, major vascular occlusion, iatrogenic injuries, and certain drugs have been implicated in this regard [4].

Drug-induced IC has previously been described in association with a number of drug groups [4]. Pseudoephedrine and phenylephrine are oral over-the-counter (OTC) decongestant agents. These drugs are commonly used to provide symptomatic relief from nasal congestion [5]. The arterial vasoconstriction caused by these agents can also rarely result in ischemic injuries to other organs, such as the colon [5]. However, published literature lacks organized data regarding oral decongestant-related IC. Therefore, to the best of our knowledge, this study represents the first systematic review of available clinical evidence evaluating the association between oral decongestant use and acute IC. After the Combat Methamphetamine Act (CMEA) ruling in 2005 and Health Canada's warning in 2016 on the risk of pseudoephedrine-induced IC, phenylephrine has largely replaced OTC usage of pseudoephedrine as a decongestant agent [6,7]. While this drug has a relatively lower propensity to cause vasoconstrictive complications, it may still culminate in serious adverse effects like IC. Cases of reversible IC are frequently ignored and remain undiagnosed in clinical practice. As a result, it is possible that oral decongestant-related IC has also been under-recognized. Our article may therefore help to increase public awareness, which will aid clinicians promptly recognize this important side effect of using oral decongestants.

2. Methods

2.1. Data abstraction

In this article, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used [8]. We searched medical databases such as MEDLINE, Google Scholar, Scopus, and Embase. The published articles in the English language were considered. The latest search date was July 20, 2022. In order to identify the relevant studies, we used a specific set of medical terminologies. The search keywords, including "IC," "colonic ischemia," "intestinal ischemia," "bowel ischemia," "acute ischemia," "colon," "drug-induced IC," "adverse drug reaction," and "IC," were combined using the Boolean operators 'AND' and 'OR' with the terms "decongestant," "phenylephrine," and "pseudoephedrine," with all associated permutations.

Four authors independently screened the results of the initial search for relevant studies. Moreover, the abstracts from major gastroenterology and endoscopy scientific meetings and

conferences were searched without the application of specific date and geographic filters. The bibliography lists were also manually screened. The initial search of the databases and reference lists resulted in a total of 214 articles.

2.2. Eligibility and inclusion in analysis

In order to determine eligibility, 3 authors independently reviewed all retrieved studies. Only the articles based on human subjects over 18 years of age were included. The reports based on non-English, redundant, duplicate, bench research, and pediatric data were excluded. The eligibility conflicts were resolved with mutual consensus. The final inclusion was made after consultation with the senior author. A total of 13 articles were included in the final comparative analysis.

2.3. Data Collection and Statistical Analysis

The data were validated by 2 authors who independently re-reviewed the full-text versions of the included papers. Patient demographics, hospital admission parameters, the clinical course of the illness, and clinical outcomes were studied and summarized. The PRISMA flow diagram outlines our search strategy for data synthesis and comparative analysis (Figure 1). The descriptive

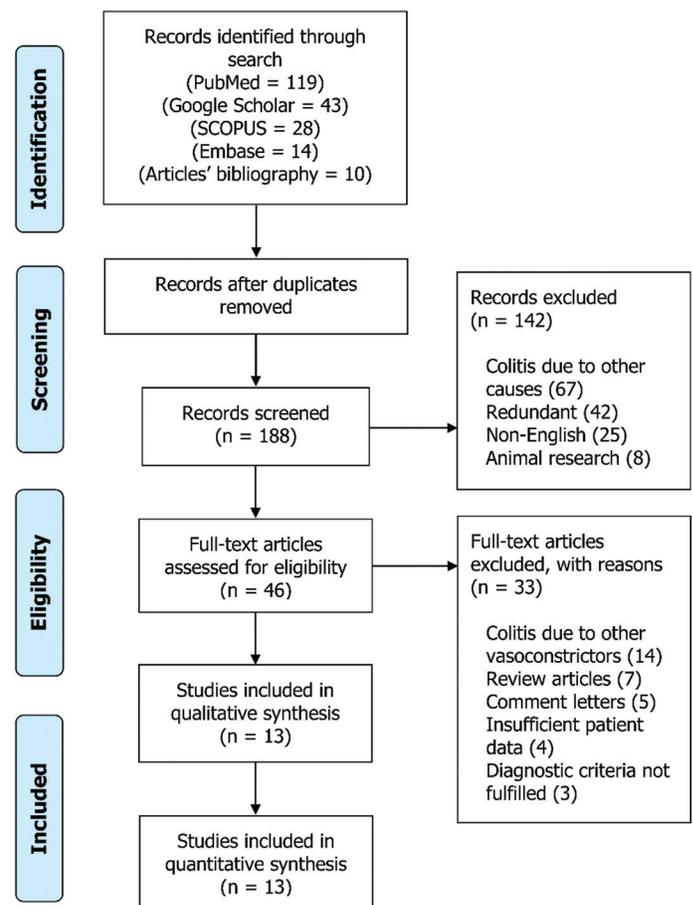


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram showing the search methodology for data synthesis regarding acute ischemic colitis secondary to oral decongestants.

patient data were presented as mean with standard deviation, range, or percentage, as applicable. The odds ratios were calculated to determine the recurrence risk in patients who were exposed to an oral decongestant agent and developed IC.

3. Results

3.1. Patients demographics

A total of 18 case reports (clinical evidence level: IV) of acute IC were identified in association with the use of pseudoephedrine and phenylephrine [9-21]. The reports were dated from 1995 to 2021. The culprit agents included pseudoephedrine in 15 (83.3%) and phenylephrine in 3 (16.7%) cases. The mean age of the patients was 51.6 ± 15.3 years, ranging from 23 to 81 years. It was notable that 14 (77.8%) patients were below the age of 60 years. A clear female gender predominance was noted, as 14 (77.8%) cases were reported in women. Information on the racial background was available in 13 cases. Of these, 6 (46.2%) patients were White, 3 (23.1%) were Caucasian, 3 (23.1%) were East Asian, and 1 (7.7%) was African American. With regard to geographical distribution, all cases were reported from 3 countries, including the United States 13 (72.2%), Korea 3 (16.7%), and Australia 2 (11.1%).

3.2. Comorbidities

The medical history showed that 5 (27.8%) of 18 patients were previously healthy, with no prior underlying medical conditions. In the remaining 13 (72.2%) patients, hypertension was reported in 6 (46.2%), a history of tobacco use in 5 (38.5%), psychiatric illnesses in 4 (30.8%), respiratory allergies in 4 (30.8%), sinusitis in 2 (15.4%), and lipid disorders in 2 (15.4%) patients. Notably, 6 (33.3%) of 18 patients were peri- or post-menopausal women. Hormone replacement therapy was reported in 2 (11.1%) patients. Pertinently, 17 (94.4%) patients had normal bowel habits before the current presentation. Only 1 (5.6%) patient experienced drug-related constipation following tramadol usage. Therefore, none of the patients had a positive history of irritable bowel syndrome in the published physician reports. Case-to-case variations were commonly noted with regard to the usage of OTC products. The patients included in our review often used products such as Sudafed, Nucosef, Claritin-D, DayQuil LiquiCaps, and Allegra-D.

3.3. Presentation patterns and diagnosis

Major clinical presentations were related to abdominal pain 16 (88.9%) and/or hemochezia 15 (83.3%). Other presenting symptoms included abdominal cramps 5 (27.8%), nausea 3 (16.7%), vomiting 3 (16.7%), diarrhea 3 (16.7%), dizziness 1 (5.6%), and/or sweating 1 (5.6%). The common clinical signs included abdominal tenderness 10 (55.6%), orthostatic changes 3 (16.7%), and abdominal distension 2 (11.1%). Laboratory data were available for 14 (77.8%) patients. In blood workup of these patients, leukocytosis 13 (92.8%) was the most common finding. Diagnostic investigations included a combination of

computed tomography (CT) abdomen and pelvis and colonoscopy in 10 (55.6%), colonoscopy alone in 6 (33.3%), and flexible sigmoidoscopy in 1 (5.6%) patient. Colonoscopy revealed the involvement of different segments of the colon: the descending 9 (50%), sigmoid 8 (44.4%), and/or splenic flexure 7 (38.9%). Colonoscopic biopsy was the mainstay of the diagnosis. The tissue diagnosis confirmed IC in 15 (83.3%) patients (Table 1).

3.4. Causality assessment

The Naranjo score was used for causality assessment in these patients. Our analysis revealed a mean value of 7.5 ± 1.3 . The score ranged from 6 to 11. We examined the individual characteristics of each case to assess whether these patients were correctly diagnosed with decongestant-induced IC. A temporal relationship was noted between the onset of colitis symptoms and oral decongestant use, denoting the potential association. The mean onset delay was 7.56 ± 7.05 days, ranging from 1 to 30 days. Furthermore, a clear dose-effect relationship and resolution of symptoms after drug cessation further supported decongestant use as the etiology of IC in these patients. The exclusion of alternative etiologies is important for the detection of drug-induced acute IC. In our review, the exclusion of probable causes was performed in all the patients.

3.5. Clinical management and outcomes

All patients received initial supportive treatment. It included intravenous fluids, antidiarrheal drugs, analgesics, and bowel rest. Two (11.1%) patients also required concurrent antibiotic therapy. The empirical antibiotics included metronidazole and ciprofloxacin [10]. Surgical intervention was reported in 1 (5.6%) patient. Klestov *et al.* reported the case of a patient with recurrent IC who underwent right hemicolectomy in her first hospitalization and then ileocolic resection in her second hospitalization [11]. The clinical outcomes were favorable. The length of the hospital stay was variable. The mean duration of hospitalization was 5.6 ± 2.8 days (range, 3–10 days). The mean follow-up duration was 17.5 ± 28.2 months (range, 1–96 months) (Table 2).

3.6. Recurrence risk

The overall recurrence rate was 22.2%. A forest plot was used to assess the effect size (odds ratio) of factors associated with recurrence of IC following oral decongestant usage. We report that patient age, female gender, and prior conservative therapy had a lower association, whereas increased dose of oral decongestants and prior sigmoid colon involvement had a higher association with acute IC recurrence, without statistical significance (Figure 2).

4. Discussion

To our knowledge, this is the first systematic review evaluating an association between oral decongestants and acute IC. It illustrates that clinicians should consider IC among the differentials in patients presenting with unexplained colitis symptoms after the use of pseudoephedrine or phenylephrine.

Table 1. Patient characteristics in cases of acute ischemic colitis secondary to the use of oral decongestants.

Authors, year	Age/ Gender	Country, ethnicity	Clinical presentation	Comorbid conditions	Bowel habits	OTC oral decongestant containing product	Exposure time	Abnormal laboratory findings	Diagnostic investigation	Affected colon
Schneider, 1995 [9]	58/F	USA	Cramping abdominal pain, rectal bleeding	Previously healthy, HRT >15 years	Normal	Efidac/24 (pseudoephedrine 240 mg daily)	5 days	WBC 12,500/uL, hematocrit 43%	Colonoscopy	Upper sigmoid colon
Dowd et al., 1999 [10]	37/F	USA, White	Lower abdominal cramps, 60 episodes of bloody diarrhea	Sinusitis, depression, hypercholesterolemia, acne, former smoker, perimenopausal	Normal	Sudafed-D (pseudoephedrine 30 mg, acetaminophen 500 mg) twice daily	7 days	WBC 18.7 × 10 ⁹ /L	Flexible sigmoidoscopy	20 cm from the anal verge to 8 cm into the distal transverse colon
Dowd et al., 1999 [10]	44/F	USA, White	Left-sided abdominal pain	Previously healthy, perimenopausal	Normal	Sudafed Plus Allergy (containing 30 mg pseudoephedrine) 2–3 times daily	7 days	WBC 12.0 × 10 ⁹ /L	Colonoscopy	Splenic flexure to the descending colon
Dowd et al., 1999 [10]	46/F	USA, White	Lower abdominal pain associated with bloody stools	Chronic sinusitis, allergic rhinitis, perimenopausal on HRT	Normal	Trinalin (azataidine maleate 1 mg and pseudoephedrine sulfate 120 mg)	6 days	WBC 13.3 × 10 ⁹ /L, ANA 1:40	Colonoscopy	Sigmoid to the splenic flexure
Dowd et al., 1999 [10]	50/F	USA, White	Abdominal pain and passage of 9 bright red stools per rectum	Ulcerative colitis quiescent for 10 years, perimenopausal	Normal	30 mg pseudoephedrine, 500 mg acetaminophen, and 2 mg chlorpheniramine maleate twice daily	7 days	WBC 15.0 × 10 ⁹ /L	Colonoscopy	Splenic flexure from 35–48 cm
Klestov et al., 2001 [11]	51/F	Australia, Caucasian	Colicky abdominal pain, vomiting, hematochezia	HTN, tension headaches, depression, left-knee osteoarthritis, right hemicolectomy	Normal	Nucosel daily (14.9 mg codeine + 60 mg pseudoephedrine) for 2 years and 900 mg daily pseudoephedrine before each hospitalizations	2 years	WBC 18.5 × 10 ⁹ /L, ESR 93 mm/h, CRP 33 mg/L	Laparotomy	Right colon and terminal ileum
Lichtenstein and Yee, 2000 [12]	33/M	USA	Lower abdominal cramps, diarrhea, hematochezia	Chronic asthma on albuterol and corticosteroid inhalers	Normal	Sudafed (pseudoephedrine HCl 120 mg) twice daily	5 days	Not reported	Colonoscopy	Descending colon
Tramo et al., 2004 [13]	46/M	Australia, White	Abdominal pain, bloody stools, dizziness, nausea, sweating	Chronic low back pain, tramadol 150 mg/day, diazepam 5 mg/day, and celecoxib 200 mg/day, smoking cessation 10 years	Tramadol- related constipation	Pseudoephedrine HCl 30 mg, dextromethorphan hydrobromide 10 mg, guaifenesin 100 mg, and acetaminophen 250 mg	7 days	Normal results	Colonoscopy	Descending colon below the splenic flexure
Ward et al., 2014 [14]	70/F	USA, African American	Nausea, vomiting, lower abdominal pain (cramping), and hematochezia	HTN, HLD, HPT, PTX, diverticulosis, glaucoma, PTSD, Remote 5-pack-year smoking	Normal	Phenylephrine bitartrate 7.8 mg, aspirin 325 mg, and chlorpheniramine maleate 2 mg	Not reported	WBC 22.3 × 10 ⁹ /L	CT abdomen and pelvis, colonoscopy	Splenic flexure, sigmoid and descending colon

(Cont'd...)

Table 1. (Continued).

Authors, year	Age/Gender	Country, ethnicity	Clinical presentation	Comorbid conditions	Bowel habits	OTC oral decongestant containing product	Exposure time	Abnormal laboratory findings	Diagnostic investigation	Affected colon
Sherid <i>et al.</i> , 2014 [15]	49/F	USA	Abdominal pain, bloody diarrhea, nausea	Allergic rhinitis	Normal	Sudafed (Pseudoephedrine) 120 mg twice daily	5 days	WBC $13.1 \times 10^9/L$	CT abdomen and pelvis, colonoscopy	Sigmoid and descending colon
Lee <i>et al.</i> , 2014 [16]	79/F	Korea, East Asian	Colicky abdominal pain followed by hematochezia	HTN	Normal	Pseudoephedrine	14 days	Not reported	CT abdomen and pelvis, colonoscopy	Colonic ischemia
Lee <i>et al.</i> , 2014 [16]	81/F	Korea, East Asian	Colicky abdominal pain followed by hematochezia	HTN	Normal	Pseudoephedrine	14 days	Not reported	CT abdomen and pelvis, colonoscopy	Colonic ischemia
Lee <i>et al.</i> , 2014 [16]	53/M	Korea, East Asian	Colicky abdominal pain followed by hematochezia	Previously healthy	Normal	Pseudoephedrine	7 days	Not reported	CT abdomen and pelvis, colonoscopy	Colonic ischemia
Ambesh <i>et al.</i> , 2017 [17]	56/F	USA	LLQ abdominal pain, hematochezia	GERD, HTN, hemorrhoids, stopped smoking 3 years ago, postmenopausal	Normal	Pseudoephedrine hydrochloride, 10 mg 4 times a day	30 days	WBC 9.7 K/mL, serum lipase 11 IU/L, ALP 108 IU/L, stool hemocult +	CT abdomen and pelvis, colonoscopy	Distal descending and sigmoid colon
Aziz <i>et al.</i> , 2018 [18]	54/F	USA, Caucasian	Hematochezia, LLQ abdominal pain	Previously healthy	Normal	10 mg pseudoephedrine 4 times daily	1 day	Hemoglobin 11.5 mg/dL, hematocrit 34.5%, ESR 31 mm/hr, CRP 2.15 mg/dL	CT abdomen and pelvis, colonoscopy	Sigmoid colon, descending colon and splenic flexure along with internal and external hemorrhoids
El-Alali and Alhmoud, 2019 [19]	34/M	USA, White	Lower abdominal pain (cramping), hematochezia	Smokeless tobacco use, BMI 43 kg/m ²	Normal	Phenylephrine HCl 5 mg, acetaminophen 325 mg, and dextromethorphan hydrobromide 10 mg	2 days	WBC $11.9 \times 10^9/L$	CT abdomen and pelvis, colonoscopy	Splenic flexure, sigmoid and descending colon
Shehata <i>et al.</i> , 2019 [20]	64/F	USA	LLQ pain, hematochezia, afebrile, normotensive	HTN, seasonal allergies, Allegra-D-related colonic ischemia	Normal	Claritin-D (loratadine and pseudoephedrine)	2 days	Hemoglobin 14.9 g/dL, WBC 15,100/mL	CT abdomen and pelvis, colonoscopy	Sigmoid area
Goraya <i>et al.</i> , 2021 [21]	23/F	USA, Caucasian	LLQ pain, hematochezia	Previously healthy	Normal	Phenylephrine HCl 10 mg, acetaminophen 650 mg, and dextromethorphan hydrobromide 20 mg	3 days	WBC $14.3 \times 10^9/L$	CT abdomen and pelvis, colonoscopy	Descending colon

OTC: Over the counter; HRT: Hormone replacement therapy; LLQ: Left lower quadrant; WBC: White blood cell; BMI: Body mass index; HLD: Hyperlipidemia; HPT: Hyperparathyroidism; PTX: Total parathyroidectomy; PTSD, Post-traumatic stress disorder; CT: Computed tomography

Table 2. Clinical outcomes of acute ischemic colitis associated with oral decongestant use

Authors	Biopsy-proven IC	Associated findings	Other etiologies excluded	Treatment	Rechallenge	Naranjo score	Clinical outcome, hospital stay (days)	Follow-up duration	Recurrence
Schneider, 1995 [9]	Yes	Not reported	Yes	Conservative treatment	No	6	Resolved	Not reported	No
Dowd et al., 1999 [10]	Yes	LLQ cramps, tenderness, rectal blood	Yes	Empirical metronidazole and ciprofloxacin; supportive therapy	No	7	Resolved, 3 days	12 months	No
Dowd et al., 1999 [10]	No	Orthostasis	Yes	Supportive treatment	No	7	Resolved, 3 days	10 months	No
Dowd et al., 1999 [10]	Yes	Orthostasis, abdominal tenderness, guaiac-positive stool	Yes	Misdiagnosed in the first episode then treated supportively and Trinalin cessation	No	8	Resolved	12 months	Yes
Dowd et al., 1999 [10]	Yes	Abdominal tenderness, rectal blood	Yes	Conservative treatment	No	7	Resolved	1 month	No
Klestov et al., 2001 [11]	Yes	Peritonitis requiring emergency laparotomy	Yes	First hospitalization: Right hemicolectomy Second hospitalization: Ileocolic resection	No	10	Resolved	10 months	Yes
Lichtenstein and Yee, 2000 [12]	Yes	Not reported	Yes	Conservative treatment	No	7	Resolved	10 months	No
Traino et al., 2004 [13]	Yes	LLQ tenderness, rectal blood clots, <i>H. pylori</i> -positive	Yes	Managed conservatively	No	7	Resolved, 7 days	20 months	Yes
Ward et al., 2014 [14]	Yes	Elevated BP, LLQ tenderness	Yes	Supportive therapy	No	8	Resolved	Not reported	No
Sherid et al., 2014 [15]	Yes	LLQ tenderness, rectal blood	Yes	IV hydration, bowel rest and pain control	No	8	Resolved, 4 days	Not reported	No
Lee et al., 2014 [16]	No	Not reported	Yes	Supportive therapy	No	6	Resolved, 7~10 days	Not reported	No
Lee et al., 2014 [16]	No	Not reported	Yes	Supportive therapy	No	6	Resolved, 7~10 days	Not reported	No
Lee et al., 2014 [16]	No	Not reported	Yes	Supportive therapy	No	6	Resolved, 7~10 days	Not reported	No
Ambesh et al., 2017 [17]	Yes	Nonbloody, nonbilious vomiting	Yes	IV pantoprazole, morphine, clear liquid diet	No	7	Resolved	Not reported	No
Aziz et al., 2018 [18]	Yes	LLQ tenderness, rectal blood	Yes	NPO, supportive treatment	No	8	Resolved, 3 days	Not reported	No
El-Alali and Alhmoud, 2019 [19]	Yes	Distended abdomen, LLQ tenderness	Yes	Managed conservatively	No	8	Resolved	2 months	No
Shehata et al., 2019 [20]	Yes	LLQ tenderness	Yes	NPO, IV fluids, antibiotics	Yes	11	Resolved	7 years	Yes
Goraya et al., 2021 [21]	Yes	LLQ tenderness, hypoactive bowel sounds	Yes	IV fluids and antidiarrheal medication	No	8	Resolved, 4 days	2 months	No

IC: Ischemic colitis; LLQ: Left lower quadrant; BP: Blood pressure; IV: Intravenous; NPO: Nil per os

4.1. Pathogenesis

The pathogenesis of drug-induced IC may be related to mechanisms such as vasospasm, thrombosis, and shunting

of mesenteric perfusion [22]. In a systematic review, Farooq et al. showed that drugs such as cocaine, triptans, ergotamine, vasopressin and its analogs, and phenylpropanolamine can

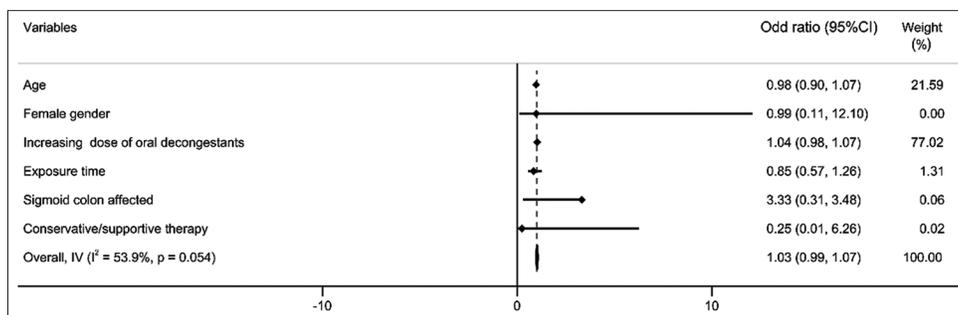


Figure 2. Forest plot showing effect size (odds ratios) of factors associated with acute ischemic colitis recurrence following oral decongestant use.

cause IC due to their strong mesenteric vasoconstrictive effects [23]. In this context, alpha-adrenergic agonists such as pseudoephedrine and phenylephrine may also precipitate IC. These drugs increase mesenteric vasoconstriction, which may trigger vasospasm and colonic ischemia in susceptible individuals. Pseudoephedrine has already been linked to marked vasoconstrictive side effects. It may even lead to myocardial infarction by causing spasm of the coronary vasculature [24]. Therefore, the likelihood of pseudoephedrine causing acute IC is higher than that of phenylephrine. This observation may be attributed to phenylephrine’s poor bioavailability because of the extensive first-pass metabolism in the gut and liver [25]. Only up to 40% of phenylephrine’s dose can reach systemic circulation, compared to 90% for pseudoephedrine [25,26]. However, in a randomized controlled trial, Atkinson *et al.* revealed that the relative bioavailability of phenylephrine 10 mg was doubled (F_{bio} 2.11, 95% CI 1.89, 2.31) when used in the combination with acetaminophen 1000 mg [27]. OTC products are often based on a combination of phenylephrine and acetaminophen. Therefore, this factor can have a role in the precipitation of phenylephrine-related colonic ischemia. It calls for increased pharmacovigilance for OTC products containing phenylephrine and acetaminophen.

4.2. Gender predisposition

IC commonly shows a female gender predilection [28,29]. In our systematic review on oral decongestants, 77.8% of patients with colonic ischemia were also women. The definitive rationale for this gender trend in patients with IC is still unclear. It can be attributed to the irregularities in the hypothalamic-pituitary-gonadal axis that often occur in women aged 35–50 years [30,31]. Consequently, hormonal changes culminate in a marked alteration in estrogen levels [31]. As the action of the estrogen hormone is mediated by acetylcholine or increased blood flow, it is a permissive vasodilator [32,33]. Therefore, transiently low levels of estrogen may potentiate the sensitivity to vasoconstrictors in females. Contrarily, increased levels of estrogen may contribute to a hypercoagulable state in women [34,35]. Due to hyperestrogenemia and the procoagulant properties of progestins, hormone replacement therapy may also have led to increased thromboembolic events early on in its use [36]. In our review, the rapid onset of symptoms

and early improvement after decongestant cessation may point to reversible mesenteric arterial vasoconstriction as the etiopathogenesis. Dowd *et al.* also implicated this causal mechanism in their report on 4 cases of pseudoephedrine-related IC involving perimenopausal women [10]. However, future research is warranted to investigate the causal link between IC, female gender, and oral decongestants.

4.3. Comorbid conditions

Colonic ischemia mostly affects elderly individuals with multiple comorbid conditions. However, it was notable that 14 (77.8%) of the 18 patients in our review were under the age of 60 years. It indicates the possibility that drug-induced IC can also be encountered in relatively younger age groups. Fernández *et al.* conducted a retrospective, case-control study, which showed that diabetes, lipid abnormalities, heart failure, peripheral vascular disease, and use of aspirin or digoxin were associated with the development of IC [37]. The findings in our review were mostly in line with the aforementioned results. The underlying conditions like hypertension, a history of tobacco use, psychiatric illnesses, respiratory allergies, sinusitis, and lipid disorders were reported. Notably, peri- or post-menopausal status in women is also important because it may predispose them to vasoconstrictor-related IC [10]. As constipation is a risk factor for IC, an inquiry about the daily bowel habits is imperative. In our review, prior to presenting with IC, all patients had regular bowel movements. Only 1 patient had drug-induced constipation. Traino *et al.* reported the case of the patient who developed pseudoephedrine-related IC and underlying tramadol-related constipation acted as a contributing factor [13].

4.4. Clinical presentation

Clinical presentation of IC is variable and nonspecific. However, a sudden-onset, cramping, lower abdominal pain, and rectal bleeding are often present [38]. While colonic ischemia can present with vague symptoms, a few telltale clinical signs can point in the right direction. Such positive findings may include segmental colitis, scant diarrhea, and minor bleeding [39]. Patients often develop abdominal tenderness, particularly at the affected colonic site. No sensitive or specific laboratory markers exist for IC. However, leukocytosis is a common finding in these patients [39]. In our systematic review, the presentation patterns

were in line with the above-mentioned trends. The patients with decongestant-induced IC frequently presented with abdominal pain and hematochezia. Leukocytosis was the most common laboratory finding, followed by low hemoglobin levels.

4.5. Diagnosis

The diagnosis of IC is predominantly based on the clinical suspicion and the workup findings. Radiological, endoscopic, and histopathological evaluations are important in this regard [40]. Clinical suspicion may aid physicians in considering IC in patients presenting with vague clinical symptomatology [40]. It is important to exclude the probable causes with overlapping clinical features [41-44]. Imaging such as abdominal radiography commonly shows nonspecific gas pattern or ileus early in the disease [44]. With the progression of the disease, submucosal hemorrhage and edema occur. These may lead to focal mural thickening, often described as “thumbprinting” [44]. A CT scan can also reveal negative findings at the beginning of the disease, but it can still help to exclude other probable etiologies [45,46]. In addition to colonic wall thickening in different segments, CT findings may often include stranding in paracolic areas [46].

Colonoscopy findings include segmental inflammation of the colon, most commonly the descending and sigmoid parts. It is characterized by the edematous, friable mucosa with overlying exudate, erythema, erosions, friability, loss of vascularity, shallow longitudinal ulceration, and mucosal bleeding [47]. The timing of the colonoscopy in relation to the start of symptoms can also aid in determining the severity of IC [47]. Early colonoscopy enables more rapid detection of ischemic stigmata, decreasing the possibility of a false positive, and avoiding potentially dangerous and needless treatment [47]. In this regard, the efficacy of rapid bowel preparation with 1 L polyethylene glycol ascorbate solution can be evaluated [48]. In patients with IC, histology often shows mucosal edema and hemorrhage [49]. However, erosions, granulation tissue hypoplasia, and macrophages with hemosiderin pigmentation extend into the submucosa in more severe cases [49]. Colonoscopic biopsy is the most sensitive and specific test for the diagnosis of IC [49]. It is considered the gold standard [49]. In our review, workup findings largely validate these observations.

Drug-induced IC remains a diagnosis of exclusion. Therefore, alternative causes should be systematically ruled out [40,50]. The Naranjo scoring algorithm can be used for causality assessment [51]. In our data, the score ranged from 6 to 11, indicating that IC was a *probable* or *definitive* drug reaction following the use of pseudoephedrine and phenylephrine. Moreover, a close temporal relationship between symptom onset and oral decongestant intake and exclusion of all alternative etiologies also played an important role in establishing diagnosis.

4.6. Clinical management

A vast majority of IC cases are transient and resolve spontaneously. Therefore, the clinical management mostly consists of bowel rest, intravenous fluids, and antidiarrheal

medications [52]. In most patients, the symptoms resolve in 1–2 days, with complete clinical resolution being attained in 2 weeks [52]. A nasogastric tube can be placed in selected patients with distension and ileus. In addition, parameters such as lactate levels and mixed venous oxygen saturation should be monitored, depending on the severity of the disease. The use of antibiotics lacks consensus in mild and self-limited cases of drug-induced IC. The American College of Gastroenterology practice guidelines recommend their use in moderate to severe disease [52]. The permanent cessation of the offending drug carries paramount importance in preventing recurrent and severe episodes of colonic ischemia. Patients should be educated about this adverse drug reaction to achieve compliance.

4.7. Clinical outcomes and recurrence risk

In our review, all patients initially recovered from IC following decongestants. Due to the self-limiting nature of the disease after the offending drug cessation, the morbidity was relatively lower. Cosme *et al.* evaluated the 5-year recurrence rate of IC, which was 9.5% [53]. Similarly, Sherid *et al.* showed a recurrence rate of IC of 8.5% after 6 years [54]. In patients with drug-associated IC, correct diagnosis in initial episode carries paramount clinical importance. It may save patients from severe, recurrent IC after reexposure to the similar drugs. Notably, the overall recurrence rate in our review was 22.2%. Patient age, female gender, and prior conservative therapy had a lower association, whereas an increased dose of oral decongestants and prior sigmoid colon involvement had a higher association with decongestant-related acute IC recurrence, without statistical significance. Most patients involved in decongestant-related IC were below 60 years of age. Females possibly had a transient presentation of IC and recovered with decongestant cessation and supportive treatment. Furthermore, increased doses of decongestants may increase their vasoconstrictive effects, which can potentiate the occurrence of severe, recurrent IC on subsequent exposure. It may point to a dose-dependency effect in gastrointestinal tolerability. However, further research is warranted in this regard.

4.8. Future directions

Mandating proper community education on the use of oral decongestants should be considered. The recognition of IC as a possible adverse effect of these drugs is clinically important. Due to the decreased efficacy of phenylephrine compared to pseudoephedrine and the control over acquiring pseudoephedrine, the chronic use of phenylephrine could increase in the following years. It may lead to an increase in systemic effects in the population. It is therefore important for policymakers to limit the OTC transactions of such medications. Moreover, clinicians should emphasize a detailed clinical history. Specific questions regarding the OTC use of pseudoephedrine or phenylephrine-based products should be asked when a patient presents with unexplained colitis symptoms. Furthermore, in patients with a history of IC or underlying risk factors such as vascular disease or concomitant use of other high-risk drugs, the

use of pseudoephedrine or phenylephrine should be completely avoided.

5. Conclusions

Acute IC following the use of pseudoephedrine and phenylephrine-based oral decongestants remains a rare clinical entity. Prompt recovery can be achieved with the early diagnosis and supportive treatment. A detailed clinical history specifically inquiring about the use of these medications is imperative for an early detection. Moreover, a precise etiology establishment is imperative to avoid subsequent exposure and recurrence in cases of drug-induced IC. Therefore, healthcare providers should maintain a high index of clinical suspicion for oral decongestant-related acute IC in patients presenting with unexplained colitis symptoms. Even though it is uncommon, this serious complication can be avoided by limiting the use of oral decongestants for mild symptoms of common cold. After initial episode of IC, patients should be educated to avoid phenylephrine and pseudoephedrine-containing OTC and herbal formulations.

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Conflicts of Interest

The authors declare that they have no conflict of interest.

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