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Research Article

A Review on Colonic Ischemia due to Vasoconstrictors

Ikechukwu Okereke[1], Belonwu Valentine Okafor[2*], Syed Burhanuddin Khadri[3], Dolly Ogwu[4], Hassaan Barkat[5], Ofure Harrison[6], Sangeetha Krishnamoorthy[7], Osazee Eguagie[4], Janet Adebukola Omole[8], Anusha Thalla[9], Iyanu Victoria Olateju[10], Matthew Oluwafemi Owolabi[10], Ogechi Lilian Okeke[1], Ufuoma Olori[11], Chisa Okachi Oparanma[11], Hemant Kumar Kattula[12]

[1]University of Nigeria Faculty of Medicine, Nigeria

[2]Nnamdi Azikiwe University College of Health Sciences, Nigeria

[3]Beihua University School of Medicine

[4]University of Benin School of Medicine, Nigeria

[5]Islamic International Medical College, Pakistan

[6]V. N Karazin Kharkiv National University, Ukraine

[7]Tianjin Medical University, China

[8]Allsaints University College of Medicine, Saint Vincent and the Grenadines

[9]Katuri Medical College, India

[10]Washington Adventist University, USA

[11]Kharkiv National Medical University, Ukraine

[12]Avalon University School of Medicine (AUSOM), Curaçao

[*]Corresponding author: Belonwu Valentine Okafor, Department of Internal Medicine, Nnamdi Azikiwe University College of Health Sciences, Nigeria

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Abstract

Intestinal ischemia results due to reduced blood flow to the intestine. Hypoperfusion of mesenteric vasculature can be due to occlusive or nonocclusive etiology. Nonocclusive mesenteric ischemia (NOMI) is due to arterial spasm from vasoconstrictors. Colon ischemia has a reported mortality rate ranging from 6 to 25%, depending upon the causal agent and comorbidities. This review's scope was to examine the body of published literature regarding outcomes of iatrogenic NOMI and compare cocaine-related NOMI with other causes of iatrogenic large bowel ischemia.

A literature search was conducted on Pubmed and Google scholar, using "Mesenteric Ischemia" and "Vasoconstrictor" as the Mesh terms. Twenty-two articles (19 case reports, 3 case series) were finally included in our review. Among study subjects, Abdominal pain was the presenting complaint in 88.88% of patients, and bloody bowel movements were reported in 81.48% of patients. Diagnostic modalities used included colonoscopy (59.26%), sigmoidoscopy (23.07%), computed tomography (37.04%), plain abdominal films (11.54%), and laparotomy (19.23%). Combining findings from all the diagnostic modalities revealed pan-colonic involvement in 11.54% of patients, proximal colon in 23.08% of patients, 7.68% of patients had involvement of transverse colon and descending/ sigmoid colon were involved in 55.56%. Splenic flexure region involvement was noticed in 30.77% of cases. Most of the patients had more than one region of bowel involved. Findings of severe colon ischemia, including ulcers, hemorrhages, and gangrene, were found in 70.37% of patients on colonoscopy or autopsy. Nineteen patients (70.37%) were managed conservatively with broad-spectrum antibiotics, intravenous fluids, and bowel rest. Two of them died due to septic shock, while the remaining 17 recovered without any further complications. Eight patients (29.63%) required surgical management, and two of them had septic shock, causing death.

In this series, nonoperative management had a success rate of 89%, while surgical management had a success rate of 75%. Based on the available reported dataset, mean hospitalization days for patients managed non-operatively were 4.31 (Range 2-10). For patients requiring surgery, it was 21 (range 4-60) due to sepsis and multiorgan failure, complicating the colon ischemia and prolonging the stay. Significant differences were found between cocaine and non-cocaine vasoconstrictor-induced large bowel NOMI regarding surgery and length of hospital stay (7 days vs 4 days), but the difference in mortality and hospital score did not reach statistical significance. Our article's message is that in patients with acute abdominal pain where a diagnosis of colon ischemia is being entertained, care should be taken not to miss out on the potential role of vasoconstrictors, including cocaine.

Keywords: Colon Ischemia; Vasoconstrictors

1. Introduction

Intestinal ischemia results from an insult that causes reduced blood flow to a level inadequate to meet the oxygen and nutrients demand required for cellular metabolism [1]. It can be caused by hypoperfusion of mesenteric vasculature due to occlusive or nonocclusive etiology. Occlusive etiologies include embolic or thrombotic arterial occlusion and venous thrombosis. Nonocclusive mesenteric ischemia (NOMI) results from severe mesenteric arterial hypoperfusion with secondary arterial spasm due to several causes, including hypovolemia, heart failure, shock, vasoconstrictors, and severe liver or renal disease. Patients with acute colonic ischemia usually present with rapid onset of cramping abdominal pain and tenderness over the affected bowel, often involving the left side [2].

The differential diagnosis of colonic ischemia is broad and includes small bowel ischemia, infectious colitis, inflammatory bowel disease, and many other causes for abdominal pain and lower gastrointestinal bleeding. Treatment depends on the severity and etiology of colonic ischemia. It resolves in most patients with supportive care, including nasogastric tube insertion, nutritional support, antibiotics, antithrombotic therapy if occlusive ischemia, and abdominal exploration if signs of colonic infarction and necrosis are present [3]. The prognosis of patients with ischemic colitis depends upon the etiology, disease severity, distribution, and comorbidities [3].

2. Methods

2.1 Data abstraction

A literature search was conducted on PubMed using "Mesenteric Ischemia' and 'Vasoconstrictor" as the Mesh terms. For inclusion in this review, the patient discussed must have a diagnosis of large bowel ischemia with vasoconstrictor as its etiology. Of the articles generated through the search, 50 were for the large colon. Articles were excluded if patients had a secondary or significant concomitant reason to develop colon ischemia (e.g. adhesions, volvulus, serotonin syndrome, or any other definite etiology causing septic shock) to avoid bias. Pharmacologic agents causing colon ischemia by means other than vasoconstriction were also excluded.

The study design was simplified to case reports or case series. Patient-specific information was recorded for age, gender, race, smoking status, type of vasoconstrictor, colonoscopic findings, and whether a surgical procedure was required during the hospital or not. Cocaine use was confirmed by either a positive urine drug screen or from history taken from the patients. Data related to colonoscopic findings were recorded for the presence or absence of hemorrhages. Also, patterns of colon ischemia were evaluated by colonoscopy reports, CT images, or surgical findings.

To avoid potential bias while investigating intestinal ischemia due to vasoconstrictors, studies with small-intestinal colon ischemia were excluded due to the extensive blood supply of the small intestine through multiple jejunal and ileal arteries, which then go on to form an extensive anastomotic network and arterial arcades before supplying intestinal wall.

2.2 Objectives

The study's primary outcomes were mortality and hospital length of stay (LOS), while secondary outcomes included the need for surgery, LACE index, and Hospital score.

2.3 Baseline characteristics

The initial search yielded 59 manuscripts for large bowel ischemia, all of which were screened for inclusion. Forty-eight manuscripts were eligible for critical evaluation, and ultimately 22 articles met the inclusion criteria. Of these 22 articles, 19 were case reports, and 3 were case series (Table 1).

Among study subjects, 92% of the patients were young (age <65), 27% were of white ethnicity, and 37% were males. Smoking history was absent in 85% of the patients. Abdominal pain was reported in 88.88% of patients, and bloody bowel movements were reported in 81.48% of patients. Diagnostic modalities used included colonoscopy (59.26%), sigmoidoscopy (23.07%), computed tomography (37.04%), plain abdominal films (11.54%), and laparotomy (19.23%). Combined findings from all the diagnostic modalities revealed pan-colonic involvement in 11.54%, proximal colon in 23.08%, transverse colon in 7.68%, and descending colon and sigmoid colon in 55.56%. Splenic flexure region involvement was noticed in 30.77% of cases.

Most of the patients had more than one region of bowel involved. Findings of severe colon ischemia including ulcers, hemorrhages, and gangrene, were found in 70.37% of patients on colonoscopy or autopsy. Nineteen patients (70.37%) were managed conservatively with broad-spectrum antibiotics, intravenous fluids, and bowel rest. Two of them died due to septic shock, while 89.47% recovered without any further complications. Eight patients (29.63%) required surgical management, and two of them suffered from septic shock, causing death. In this series, nonoperative management had a success rate of 89%, while surgical management had a success rate of 75%. Based on the available reported dataset, mean hospitalization days for patients managed non-operatively were 4.31 (Range 2-10).

For patients requiring surgery, it was 21 (range 4-60) due to sepsis and multiorgan failure, complicating the colon ischemia and prolonging the stay. The clinical features, evaluation, and outcomes of the involved patients have been summarized in Table 1.

Sr No	Author Name	No of patients	Vasoconstrictor used	Indication	Symptoms experienced	Location	Diagnosis	Reversibility	Risk Factor	Hospital Score {risk of 30-Day potentially avoid-able readmission}	Hospitalization days	Surgery performed
1	Stillman et al. (6)	1	Ergotamine tartrate	Dizziness	Crampy abdominal pain and hematochezia	Distal transverse colon and proxy-mal part of distal colon	Barium enema	Yes	NA	3{low, 5.8%}	2	No
2	Lambert et al. (7)	1	IV Vasopressin	Esophageal variceal bleed	Hematochezia but no abdominal pain	Rectosigmoid junction and splenic flexure	Colonoscopy	Yes	NA	0 {low, 5.8%}	3	No
3	Johnson et al (8)	1	Phenylpropranolamine	Weight loss	Severe RLQ abdo-minal pain with bloody diarrhea	Proximal and mid-transverse colon	NA	Yes	Non obstructtive Colonic ischemia	4 {low, 5.8%}	NA	Yes
4	Fishel et al. (9)	1	Cocaine	NA	RLQ abdominal pain, nausea, diarrhea, vomiting, watery hemoccult positive stools	Cecum and ascending colon	Abdominal roentgenograms, gastrogr-afin enema, laprotomy	No	NA	4{low, 5.8%}	NA	Yes
5	Nalbandian et al. (10)	1	Cocaine	NA	Diffuse abdominal pain, bloody stools.	Ascending colon	Laprotomy	No	NA	NA	60	Yes
6	Schmit	1	Glypres	Massive	Bloody stools	Ascending	Laparoscopy	No	NA	NA	NA	No

	t et al. (11)		sin	hematemesis from cirrhosis		colon	and biopsy					
7	Rogers et al. (12)	1	Ergotamine	Migraine	Severe abdominal pain, nausea, vomiting and fever	Pancolonic	Arteriogram	No	NA	NA	NA	No
8	Yang et al. (13)	1	Cocaine	NA	Hematochezia and bloody stool.	From rectosigmoid junction to splenic flexure	Colonoscopy	Yes	NA	2 {low, 5.8%}	4	No
9	Endress et al. (14)	2	Cocaine	NA	RLQ abdominal pain, bloody diarrhea, muscle rigidity, and fever	Transverse and ascending colon, splenic flexure to cecum, small bowel	Colonoscopy and biopsy	Reversible in one patient, surgery perfoormed in the second patient.	Smoking crack cocaine	2 {low, 5.8%}	5, 7	No, Yes
10	Rutgeerts et al. (15)	1	Dihydroergotamine	Migraine	Diffuse abdominal pain and profuse watery diarrhea mixed with blood	Splenic flexure and proximal colon	Colonoscopy	Yes	OCP's	0 {low, 5.8%}	2	No
11	Brown et al. (16)	1	Cocaine	NA	LLQ pain with hematochezia	Sigmoid colon	Flexible Sigmoidoscopy	No	Diabetes and Hypert-ension	4 {low, 5.8%}	20	Yes
12	Knudsen et	2	Sumatriptan	Migraine	Crampy LLQ abdominal pain,	Descending colon, sigmoid	Colonoscopy with biopsy	Yes	Cigarette smoking	4 {Low, 5.8%} 4 {Low, 5.8%}	5, 5	No, No

	al. (17)				hematochezia	colon						
13	Dehesa et al. (18)	1	Cocaine	NA	Severe abdominal pain, confusion, agitation, bloody stools	Ascending colon and cecum	CT scan, laparotomy	No	NA	4 {low, 5.8%}	NA	Yes
14	Payne et al. (19)	1	Ergotamine tartrate	Migraine	Abdominal pain, anorexia, and weight loss	Left colon	Abdominal CT, laparotomy	No	NA	NA	4	Yes
15	Linder et al. (20)	3	Cocaine	NA	NA	Left descending colon	CT abdomen with contrast, colonoscopy with biopsy, flexible sigmoidoscopy	Reversible in the first and second patient. The third patient died 2 weeks after the initial examination	Cigarette smoking 1 pack for last 5 years in 1 patient, Hypertension in the other patient.	1 {low, 5.8%} 1 {low, 5.8%} 2 {low, 5.8%}	3, 14 and 7	No, No, Yes
16	Naik et al. (21)	1	Sumatriptan	Migraine	Crampy abdominal pain, bloody diarrhea, fever	Splenic flexure	CT scan, colonoscopy with biopsy	No	NA	2 {low, 5.8%}	NA	No
17	Schwartz et al. (22)	1	Naratriptan	Migraine	Hematochezia and lower abdominal pain	Splenic flexure	Colonoscopy with biopsy	Yes	NA	0 {low, 5.8%}	4	No
18	Moawad et al. (23)	1	Sumatriptan	Migraine	Crampy LLQ abd pain, diarrhea, hematochezia	Descending colon	CT, flexible sigmoidoscopy,	Yes	NA	0 {low, 5.8%}	Not reported	No

19	Hodge et al. (24)	1	Sumatriptan	Migraine	Abdominal pain, nausea	Sigmoid colon	Colonoscopy with biopsy, CT abdomen with contrast	Yes	NA	1 {low, 5.8%}	4	No
20	Westgeest et al. (25)	1	Naratriptan	Migraine	Lower abdominal pain and hematochezia	Descending colon	Colonoscopy CT abdomen and mesenteric angiography	Yes	NA	2 {low, 5.8%}	4	No
21	Nguyen et al. (26)	1	Sumatriptan	Migraine	LLQ abdominal pain, nausea, vomiting, bloody diarrhea, diaphoresis, tenesmus	Splenic flexure, descending colon to sigmoid colon	CT scan, colonoscopy with biopsy, Magnetic Resonance Angiography	Yes	NA	3 {low, 5.8%}	10	No
22	Akbar et al. (27)	1	Naratriptan	Chronic migraine	Crampy lower abdominal pain, bloody diarrhea, nausea	Transverse colon to sigmoid colon	CT abdomen with contrast, colonoscopy with biopsy	Yes	NA	3 {low, 5.8%}	5	No

Table 1: Demographics of involved patients.

3. Results

Outcome indices that we used included the hospital score, mortality, hospital length of stay, and requirement for surgery [34]. Hospital score predicts 30-day readmission risk [35]. In our subset of patients, there were significant differences between cocaine and non-cocaine vasoconstrictor-induced large bowel NOMI regarding surgery and length of hospital stay (7 days vs. 4 days), but the difference in mortality and Hospital score did not reach statistical significance. This led us to conclude that there is no true difference in the outcomes discussed for cocaine and non-cocaine vasoconstrictor-related large bowel ischemia, and both behave similarly.

Even though these vasoconstrictors have different mechanisms and different receptors to act on, all of these cause vasoconstriction of arteries resulting in hypoperfusion, and subsequently, intestinal ischemia-a theory that explains similar outcomes in terms of mortality between these groups.

4. Discussion

The most common form of intestinal ischemia is colonic ischemia, and it mostly affects older adults [28]. It results from either occlusive vascular disease or non-occlusive disease and can be gangrenous or non-gangrenous. Nonocclusive colonic ischemia is due to mesenteric arterial vasoconstriction. Colon ischemia has a reported mortality rate ranging from 6 to 25%, depending upon the causal agent and comorbidities [29, 30]. This review focuses on nonocclusive colonic ischemia caused by vasoconstrictors. The vasoconstrictors found in the literature associated with colon ischemia included cocaine, sumatriptan, naratriptan, ergotamine, ergotamine, phenyl-propanolamine, and vasopressin. Cocaine produces severe vasoconstriction of the splanchnic circulation leading to ischemia and possible infarction. Texter et al. suggested that cocaine acts on alpha-adrenergic receptors abundantly found in the ileum and colon, blocking the reuptake of released norepinephrine [31]. Triptans and ergotamine bind to the serotonin receptors (5-HT1B and 5-HT1D respectively), and these receptors are also abundantly found in the intestinal wall as described in an animal study [32]. Phenylpropanolamine has an affinity for alpha-receptors, and vasopressin binding to V1 receptors on vessels results in vasoconstriction. A hybrid case-control study by Elramah et al. described that cocaine-related ischemic colitis has a significantly higher mortality rate. The control group in the described study included individuals who met the diagnostic criteria of ischemic colitis but had no history of cocaine use and a urine test negative for cocaine [5].

Our review focused primarily on the colonic ischemia caused by vasoconstrictors and compared cocaine-related large bowel ischemia with that caused by other vasoconstrictors. Due to the increased potential of mortality and emergent need for surgery, thorough history taking of potential use of drugs causing vasoconstriction and decreased intestinal perfusion is of paramount importance. Medical providers should also look for other potential drugs associated with colon ischemia. Although most patients will have transient ischemia with non-gangrenous colitis that can be successfully managed nonoperatively, prompt recognition and surgical intervention are critical in patients with gangrenous colitis [33]. In our dataset, ischemia was reversible, requiring only conservative management in the majority of the patients (88%) in the non-cocaine vasoconstrictor group compared with 40% of patients in the cocaine group.

The most common presenting complaints of patients in our review included abdominal pain (88.88%) and bloody bowel movements (81.48%). The diagnostic modalities employed were mostly colonoscopy

(59.26%) and computed tomography imaging (37.04%). In a subset of patients, emergent surgery was indicated, and the diagnosis was confirmed via laparotomy. Splenic flexure and transverse colon (51.85%) were the most frequent sites involved. Other commonly involved sites were the distal colon (33.34%) and ascending colon (29.63%). This is due to splenic flexure's susceptibility for ischemia due to a meager number of collateral vessels, making it a watershed area. The most common vasoconstrictors were cocaine (37.04%) and triptans (37.04%). Other vasoconstrictors included in our dataset (in descending order) were: ergotamine (14.81%), vasopressin and its analogs (7.41%), and phenylpropanolamine (3.70%). The most common method of cocaine use was smoking (60%). Other methods were inhalation (20%), intravenous (10%), and oral use (10%). Among prescription vasoconstrictors, migraine was the most common indication for the use.

Limitation

The limitation of our study is that it is not powered enough to detect a difference in mortality, as mentioned earlier if the difference truly exists. Adequate sample-sized well-designed observational studies are required in the future on this topic.

5. Conclusion

Our article's message is that in those patients with acute abdominal pain where a diagnosis of colon ischemia is being entertained, care should be taken not to miss out on the potential role of vasoconstrictors, including cocaine. Significant differences were found between cocaine and non-cocaine vasoconstrictor-induced large bowel NOMI regarding surgery and length of hospital stay (7 days vs 4 days), but the difference in mortality and hospital score did not reach statistical significance. Further studies are needed to compare outcomes between the 2 groups.

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