Original Article

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Gastrointestinal Complications and its Association with Common Risk Factors of Cerebrovascular Accident: A Retrospective Observational Study from Central India

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ABSTRACT

Introduction: Patients with Cerebrovascular Accidents (CVA) may present with Gastrointestinal (GI) complications, negatively affecting the prognosis. However, the whole spectrum of GI complications in CVA patients is unknown.

Aim: To assess GI complications in CVA patients and their association with risk factors of CVA.

Materials and Methods: The retrospective, facility-based, observational study was conducted in Department of Medicine at Gandhi Medical College and associated Hamidia Hospital, Bhopal, Madhya Pradesh, India, from March 2019 to August 2021. Total 100 patients with CVA (age >13 years) were studied based on their medical records and laboratory examinations. Details on socio-demographic variables and clinical history were obtained. Detailed general and systemic examination and vitals were documented. Complete blood picture, liver function test, renal function test, lipid profile and magnetic resonance imaging scan was also performed. A Chi-square t-test was applied to assess the association of GI complications with various variables. A p-value <0.05 was considered statistically significant.

Results: Most CVA patients were males (51%). Mean age of study population was 71.49±11.46 years. A history of hypertension and diabetes mellitus was observed in 60% and 54% of cases. Constipation (43%) was the most common GI complication, followed by dysphagia (25%). No significant association of GI complications with age (p-value=0.261), gender (p-value=0.217), hypertension (p-value=0.540) and diabetes mellitus (p-value=0.257) was observed in CVA patients. However, raised serum bilirubin, serum glutamic-oxaloacetic transaminase, and serum glutamic pyruvic transaminase in 47%, 23%, and 37% cases with CVA was observed.

Conclusion: Gastrointestinal complications are commonly observed in stroke patients irrespective of stroke but are more common in patients with ischemic stroke. Constipation and dysphagia were the most common. Faecal incontinence, abdominal pain, hiccups, and melena may also be seen in patients with CVA.

Keywords: Constipation, Dysphagia, Lipid profile, Stroke

INTRODUCTION

A Cerebrovascular Accident (CVA), also called a stroke or brain attack is a medical emergency characterised by acute compromise of cerebral perfusion resulting in a neurological deficit [1,2]. The CVA may be of three types, i.e., haemorrhagic stroke, ischaemic stroke, and Transient Ischaemic Attack (TIA). About 85% of strokes are ischaemic, whereas 15% are haemorrhagic [1]. TIA is, also termed mini-stroke, is characterised by an acute episode of neurological deficit lasting for a short period, typically less than one hour. Recently the definition of TIA includes tissue-based cerebral injury rather than time-based cerebral injury [3].

The CVA is one of the leading causes of mortality and disability worldwide. Global stroke factsheet by World Stroke Organisation reported 13.7 million new stroke cases each year, and the incidence of stroke increases with advancing age [4]. Approximately, 84% of deaths occur in low-middle-income countries due to stroke [5]. In India, 1.17 million new stroke cases were reported from different parts of India in 2016, attributing to a cumulative incidence of 105 to 152 per one lakh person per year [6,7]. Mortality due to CVA was reported in 6.94 lakh cases in India [6].

Hypertension is the predominant risk factor associated with ischaemic stroke; other risk factors include diabetes mellitus, obesity, atrial fibrillation, smoking [8]. On the other hand, haemorrhagic stroke results from the bursting of cerebral vessels, which damages the brain cells by exerting pressure on them. Intracerebral haemorrhage (ICH) and subarachnoid hemorrhage are haemorrhagic stroke subtypes [9]. Hypertension is a significant risk factor for haemorrhagic stroke also. Other risk factors associated with haemorrhagic stroke include cigarette smoking, heavy alcohol consumption, liver disease, antiplatelet therapy, dyslipidemia [9].

CVA affects the neurological system, but it also leads to a wide range of systemic impairments such as a problem with swallowing, movement, speech, urination, defaecation, significantly affecting the quality of life [6]. Complications involving the gastrointestinal (GI) system are often neglected, and literature on such complications is scarce. It has been reported that approximately 50% of patients with CVA may present with minor GI complications in the form of constipation, alteration in GI motility, and dysphagia to a severe form, i.e., GI bleeding or intestinal obstruction [10,11].

The underlying mechanisms attributing to GI complications in patients following a CVA are multifactorial and possible via the brain-gut axis's disruption [12]. This axis links the central nervous system with the enteric and autonomic nervous system and helps maintain interaction and communication between the brain and GI system. The alterations in the brain-gut axis may be due to peripheral or central factors or may be due to hormones, amines, or autonomic neural dysfunctions [12].

The GI complications are often neglected in stroke patients. Commonly, GI complications have been observed in ischaemic stroke. The whole spectrum of GI complications in CVA patients is unknown. With the above background, the present study was conducted at a tertiary care centre on stroke survivors to assess the spectrum of GI complications.

MATERIALS AND METHODS

The retrospective, facility-based, observational study was conducted in Department of Medicine at Gandhi Medical College and associated Hamidia Hospital, Bhopal, Madhya Pradesh, India, from March 2019 to August 2021. Institutional Ethics Committee approval was obtained before starting the study (letter no: 541/2020).

Inclusion criteria: Patients suffering from CVA having age above 13 years were included in the study.

Exclusion criteria: Patients under age group of 13 years, those not giving written informed consent, and those not having CVA were excluded from the study.

A detailed history regarding socio-demographic variables such as age, gender, address, and contact details, were recorded in proforma. History or relevant family history, if any, was noted.

Detailed general and systemic examination, vitals such as heart rate, blood pressure, temperature, respiratory rate, oxygen saturation were documented. And any positive abnormal finding were also noted. Details of routine and special investigations, including complete blood picture, liver function test, renal function test, lipid profile, ultrasonography abdomen, and magnetic resonance imaging scan were also recorded.

STATISTICAL ANALYSIS

Data was compiled using MS Excel and analysed using IBM Statistical Package for the Social Sciences (SPSS) software version 20.0. Categorical data were expressed as frequency and proportions, whereas continuous data were expressed as mean and standard deviation. A Chi-square's test was applied to assess the association of GI complications with various variables. A p-value <0.05 was considered statistically significant.

RESULTS

The mean age of patients with CVA was 71.49±11.46 years, and the majority (28%) belonged to 71 to 80 years, followed by 61 to 70 years (26%) and more than 80 years (25%) of age, respectively. Male predominance (51%) was observed, with a male:female ratio of 1.04:1. A history of hypertension was observed in 60% of cases, whereas diabetes was observed in 54% of patients with CVA [Table/Fig-1]. In the present study, majority had lower haemoglobin (<11 gm%), however, serum creatinine, urea levels, serum bilirubin, SGOT and SGPT were raised in CVA patients along with raised triglyceride levels [Table/Fig-2].

Most common GI complication were constipation (43%), dysphagia (25%), faecal incontinence (12%) and abdominal pain (10%). Other lest common GI complications are shown in [Table/Fig-3]. There was no significant association between GI complications and various causes of infarct on MRI (p-value >0.05) [Table/Fig-4]. No significant association was found between the GI complications and risk factors of CVA [Table/Fig-5].

Parameters	Frequency
Age (years)	
<50	3
51-60	18
61-70	26
71-80	28
>80	25
Gender	
Male	51
Female	49
Hypertension	
Yes	60
No	40
Diabetes mellitus	
Yes	54
No	46

[Table/Fig-1]: Socio-demographic characteristics of study population.

Laboratory variables		N	Normal range
Complete blood count			
Haemoglobin (gm%)	>12	23	Men: 13.2 to 16.6; women: 11.6 to 15
	11-11.9	22	
	9-10.9	39	
	<9	16	
Total leucocyte count (cells/cumm)	<4000	4	4000 to 11000
	4000-11000	96	
Renal function test			
Creatinine (mg/dL)	<1.2	98	Adult men: 0.74 to 1.35 Adult women: 0.59 to 1.04
	≥1.2	2	
Urea (mg/dL)	15-45	93	6 to 24
	>45	7	
Liver function test			
Bilirubin (mg/dL)	0-1	53	1.2 for adults, 1 mg/dL for <18 years
	>1	47	
Serum glutamic-oxaloacetic transaminase (U/L)	<45	77	8 to 45
	≥45	23	
Serum glutamic pyruvic transaminase (U/L)	<45	63	7 to 56
	≥45	37	
Lipid profile			
Triglycerides (mg/dL)	>150	31	<150
	≤150	69	
Low-density lipoprotein (mg/dL)	>150	97	<100 optimal
	≤150	3	

[Table/Fig-2]: Characteristics of the study population.
Data are expressed as percentages. CBC: Complete blood count; LFT: Liver function test; LDL: Low-density lipoprotein; RFT: Renal function test; SGOT: Serum glutamic-oxaloacetic transaminase; SGPT: Serum glutamic pyruvic transaminase; TLC: Total leukocyte count

GI complications	Frequency
Abdominal pain	10
Constipation	43
Dysphagia	25
Faecal incontinence	12
Hiccups	7
Melena	3

[Table/Fig-3]: Distribution of patients according to the spectrum of gastrointestinal complications (N=100).

DISCUSSION

Though GI complications are often reported in patients with CVA, these are often neglected. The GI complications in CVA patients may range from mild to severe such as constipation, dysphagia, GI bleeding, or intestinal obstruction [7].

Advanced age is a non modifiable risk factor of ischaemic and haemorrhagic stroke [13]. In the present study, the mean age of CVA patients was 71.49±11.46 years. The majority of patients belonged to 71 to 80 years (28%). As most patients, i.e., more than 85% belonged to the elderly age group (> 60 years), age may be a confounding factor associated with GI complications in CVA patients. However, the present study observed no significant association of GI complications with age. The GI complications were higher in the elderly age group, including constipation, dyspepsia, due to age-related decline in gastric motility [14]. The present study findings are supported by the results of Minhas SV et al., in which age of 75 years or older was identified as an independent risk factor

Complications	MRI						p-value (Chi-square)
	Anterior cerebral artery infarct	Capsulogangliomic RI	Frontal infarct	Middle cerebral artery infarct	Occipital microbleed	Thalamic infarct	
Abdominal pain	2 (11.1)	4 (16.7)	1 (12.5)	3 (6.5)	0	0	0.811
Constipation	5 (27.8)	12 (50)	2 (25)	22 (47.8)	0	2 (66.7)	
Dysphagia	6 (33.3)	5 (20.8)	3 (37.5)	10 (21.7)	1 (100)	0	
Faecal incontinence	3 (16.7)	1 (4.1)	2 (25)	6 (13)	0	0	
Hiccups	2 (11.1)	0	0	4 (8.7)	0	1 (33.3)	
Melena	0	2 (8.3)	0	1 (2.2)	0	0	

[Table/Fig-4]: Association of GI complications with Magnetic Resonance Imaging (MRI).

Risk factors	GI Complication						p-value (Chi-square test)
	Abdominal pain	Constipation	Dysphagia	Faecal incontinence	Hiccups	Melena	
Age (years)							
<50	0	0	3	0	0	0	0.261
51-60	2	9	1	4	1	1	
61-70	1	13	8	0	3	1	
71-80	4	12	5	5	1	1	
>80	3	9	8	3	2	0	
Gender							
Male	7	20	13	8	1	2	0.217
Female	3	23	12	4	6	1	
Hypertension							
Yes	4	26	15	7	5	3	0.540
No	6	17	10	5	2	0	
Diabetes mellitus							
Yes	4	22	17	5	3	3	0.257
No	6	21	8	7	4	0	

[Table/Fig-5]: Association of GI complications with risk factors.

for CVA development [15]. Similarly, the median age of CVA patients in a study by Tillman H et al., was 65 years (IQR: 55 to 74 years) [16]. However, Ji R et al. reported the median age of CVA patients with GI complications as 66 years (IQR: 56-74) [17].

Gastrointestinal complications were observed in almost equal proportions of males and females (51% males and 49% females). Johnson CO et al., reported a higher prevalence of CVA in females than males (41.1 vs. 39 million respectively) [6]. Tillman H et al., observed CVA in 45% of women and 55% males [16]. Thus, present study reported CVA and associated GI complications in almost equal proportions of males and females with no significant difference in the spectrum of GI complications between males and females.

The majority of previous studies have been done on the Western population. Only a few studies highlighted the GI complications [6,16] and their associated factors in patients with CVA in the Indian scenario. Present study provides further evidences on the GI complications and their association with the classical risk factors of CVA.

Co-morbid condition, particularly hypertension, has been linked with both ischaemic and haemorrhagic stroke. Of 100 CVA patients with GI complications, 60% had associated hypertension, and 54% had diabetes. Hypertension is implicated in the pathogenesis of stroke, irrespective of the type of stroke. Ischaemic stroke or CVA infarct are commonly attributed to underlying uncontrolled hypertension, which increases the risk via lipohyalinosis and arteriolosclerosis [18]. The most common etiological mechanism in haemorrhagic stroke is also uncontrolled hypertension [19]. Nogueira RG et al., documented hypertension as a significant risk factor of stroke; other factors associated with CVA are diabetes and obesity [8]. Ji R et al., documented history of hypertension, hepatic cirrhosis, and peptic ulcer, as important predictor of CVA [17].

The MRI was done in all the cases of CVA in the current study to observe the site and type of lesion in CVA. Ischaemic infarct at various sites were the predominant findings in CVA patients, whereas haemorrhagic stroke in the form of occipital microbleed was observed in 1% of cases. Middle Cerebral Artery (MCA) Infarct (46%) and capsulogangliomic region infarct (24%) were the most common findings on MRI. The present study results were concordant to Pandian JD and Sudhan P, in which ischaemic strokes were the most common etiology in patients reporting cerebrovascular [20]. Liu X et al., and Kabi S et al., also observed findings similar to the present study; they documented ischaemic stroke to be more common than haemorrhagic stroke [21,22]. Overall, GI complications have been reported in approximately 50% of the patients with ischaemic stroke [23].

Gastrointestinal complications can be observed in approximately half of the patients with ischaemic stroke [10]. A wide spectrum of GI complications has been reported in patients with CVA. In the present study, constipation was the most common gastrointestinal complication observed in 43% of cases with CVA, followed by dysphagia (25%). The study documented faecal incontinence, abdominal pain, hiccups, and melena in a few cases. Though previous studies have not highlighted the entire spectrum of GI complications, various complications have been associated with CVA. Different underlying mechanisms have been implicated in developing gastrointestinal complications in patients following cerebrovascular accidents. Disruption of the brain-gut axis has been observed as the most predominant factor linked with GI complications in CVA patients [8,12]. This axis plays a vital role in interaction and communication between the brain and gastrointestinal system, alteration of which in CVA could be due to peripheral or central factors or to hormones, amines, or autonomic neuralgia dysfunctions [24]. The present study findings were supported by Krogh K et al., findings, in which constipation was one of the common complications observed in stroke patients [24]. Schaller BJ et al., reported dysphagia, GI dysmotility, and GI haemorrhage as the predominant GI complications in patients with

stroke [11]. The present study findings were supported by the results of Camara-Lemarroy CR et al., the authors reported GI complications to be common in patients with an acute ischaemic stroke, which is associated with adverse outcomes in such patients in the form of disability, poor neurological function, and even death [23]. Li J et al., observed constipation in 48% of patients with stroke, with constipation higher in haemorrhagic stroke compared to ischaemic stroke [25]. Fu J observed the risk factors associated with GI bleeding in stroke cases with the prevalence of GI bleeding in 8.5% cases [26].

In the present study, baseline investigations were done in all the cases with CVA. These investigations included complete blood count, LFT, RFT, and lipid profile. Among renal function tests, serum creatinine and urea levels were raised in 8% and 7% cases, respectively. However, triglycerides and LDL were studied in present study population, which were raised in 69% and 3% cases of CVA, respectively. Dyslipidemia is one of the common findings observed in stroke, characterised by increased cholesterol levels that impair the function of the endothelium of blood vessels by producing superoxide and oxygen-free radicals. These changes ultimately increase atherosclerosis in these patients [27]. The findings of the present study are supported by the results of Onwuegbuzie GA et al., in which raised LDL was observed in 13%, and triglyceride levels were increased in 43% of patients with stroke [28].

Liver function tests may depict the underlying GI complications in patients with stroke. The present study reported raised serum bilirubin, SGOT, and SGPT in 47%, 23%, and 37% cases with CVA. Muscari A et al., reported significant liver abnormalities during the acute phase of ischaemic stroke. Amongst various liver enzymes, SGOT has been directly linked with ischaemic cerebral lesions and is associated with inflammation [29]. The index study study findings are supported by Luo Y et al., who reported direct bilirubin to be significantly associated with the severity of stroke [30].

Limitation(s)

Small sample size and retrospective nature are the main limitations of the present study. There is a need of a large randomised clinical trials to provide more strength to present study findings.

CONCLUSION(S)

Gastrointestinal complications are commonly observed in stroke patients irrespective of stroke but are more common in patients with ischaemic stroke. A wide spectrum of gastrointestinal complications could be observed in patients with CVA, including constipation, dysphagia, faecal incontinence, abdominal pain, hiccups, and melena. All these complications increase morbidity as well as mortality in patients with CVA. These complications should be emphasised to ensure early diagnosis and management.

REFERENCES

[1] Members WG, Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, et al. Heart disease and stroke statistics-2016 update: A report from the American Heart Association. Circulation. 2016;133(4):e38-60.
[2] Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, et al. An updated definition of stroke for the 21st century: A statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013;44(7):2064-89.
[3] Panuganti KK, Tadi P, Lui F. Transient Ischemic Attack. [Updated 2021 Mar 24]. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2021 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459143/.
[4] World Stroke Organisation. (2020). WSO Global Stroke Fact Sheet. Available from https://www.world-stroke.org/assets/downloads/WSO_Global_Stroke_Fact_Sheet.pdf. Last accessed on 17th August 2021.
[5] Owolabi MO, Arulogun O, Melikam S, Adeoye AM, Akarolo-Anthony S, Akinyemi R, et al. The burden of stroke in Africa: A glance at the present and a glimpse into the future. Cardiovascular journal of Africa. 2015;26(2 H3Africa Suppl):S27.
[6] Johnson CO, Nguyen M, Roth GA, Nichols E, Alam T, Abate D, et al. Global, regional, and national burden of stroke, 1990–2016: A systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurology. 2019;18(5):439-58.
[7] Kamalakannan S, Gudlavalleti AS, Gudlavalleti VS, Goenka S, Kuper H. Incidence & prevalence of stroke in India: A systematic review. Indian J Med Res. 2017;146(2):175-85.
[8] Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. N Engl J Med. 2018;378(1):11-21.
[9] Unnithan AKA, Mehta P. Haemorrhagic Stroke. [Updated 2021 Jan 16]. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2021 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK559173/.
[10] Ullman T, Reding M. Gastrointestinal dysfunction in stroke. Semin Neurol. 1996;16:269-75.
[11] Schaller BJ, Graf R, Jacobs AH. Pathophysiological changes of the gastrointestinal tract in ischemic stroke. Am J Gastroenterol. 2006;101:1655-56.
[12] Karakuła-Juchnowicz H, Dzikowski M, Pelczarska A, Dzikowska I, Juchnowicz D. The brain-gut axis dysfunctions and hypersensitivity to food antigens in the etiopathogenesis of schizophrenia. Psychiatr Pol. 2016;50(4):747-60.
[13] Boehme AK, Esenwa C, Elkind MSV. Stroke Risk Factors, Genetics, and Prevention. Circ Res. 2017;120:472-95.
[14] Dumic I, Nordin T, Jecmenica M, Stojkovic Lalosevic M, Milosavljevic T, Milovanovic T. Gastrointestinal tract disorders in older age. Can J Gastroenterol Hepatol. 2019;2019:6757524.
[15] Minhas SV, Goyal P, Patel AA. What are the risk factors for cerebrovascular accidents after elective orthopaedic surgery. Clin Orthop Relat Res. 2016;474(3):611-18.
[16] Tillman H, Johnston SC, Farrant M, Barsan W, Elm JJ, Kim AS, et al. Risk for major hemorrhages in patients receiving clopidogrel and aspirin compared with aspirin alone after transient ischemic attack or minor ischemic stroke: A secondary analysis of the POINT randomized clinical trial. JAMA Neurol. 2019;76(7):774-82.
[17] Ji R, Shen H, Pan Y, Wang P, Liu G, Wang Y, et al. Risk score to predict gastrointestinal bleeding after acute ischemic stroke. BMC gastroenterology. 2014;14(1):01-09.
[18] Shi Y, Wardlaw JM. Update on cerebral small vessel disease: A dynamic whole-brain disease. Stroke Vasc Neurol. 2016;1(3):83-92.
[19] Hanley DF, Awad IA, Vespa PM, Martin NA, Zuccarello M. Haemorrhagic stroke: introduction. Stroke. 2013;44(6 Suppl 1):S65-66.
[20] Pandian JD, Sudhan P. Stroke epidemiology and stroke care services in India. J Stroke. 2013;15(3):128-34.
[21] Liu X, Yan L, Xue F. The associations of lipids and lipid ratios with stroke: A prospective cohort study. J Clin Hypertens (Greenwich). 2019;21(1):127-35.
[22] Kabi S, Padhy R, Panda BN, Rath SN, Padhy RN. A study on clinical and laboratory profiles of haemorrhagic and ischemic strokes in an Eastern Indian teaching Hospital. Int J Res Med Sci. 2017;5:2419-21.
[23] Camara-Lemarroy CR, Ibarra-Yruegas BE, Gongora-Rivera F. Gastrointestinal complications after ischemic stroke. J Neurol Sci. 2014;346:20-45.
[24] Krogh K, Christensen P, Laurberg S. Colorectal symptoms in patients with neurological diseases. ACTA Neurologica scandinavica. 2001;103(6):335-43.
[25] Li J, Yuan M, Liu Y, Zhao Y, Wang J, Guo W. Incidence of constipation in stroke patients: A systematic review and meta-analysis. Medicine (Baltimore). 2017;96(25):e7225.
[26] Fu J. Factors affecting the occurrence of gastrointestinal bleeding in acute ischemic stroke patients. Medicine (Baltimore). 2019;98(28):e16312.
[27] Bhalla A, Gupta OP, Gupta SB. Predicting mortality in stroke. Neurol India. 2002;50(3):279-81.
[28] Onwuegbuzie GA, RengRifkatu S. Serum Lipid Profile of Patients with Ischemic Stroke in A Tertiary Centre in Nigeria. IOSR Journal of Dental and Medical Sciences (IOSR-JDMS). 2016;15(11):60-64.
[29] Muscari A, Collini A, Fabbri E, Giovagnoli M, Napoli C, Rossi V, et al. Changes of liver enzymes and bilirubin during ischemic stroke: Mechanisms and possible significance. BMC neurology. 2014;14(1):01-08.
[30] Luo Y, Li JW, Lu ZJ, Wang C, Guan DN, Xu Y. Serum bilirubin after acute ischemic stroke is associated with stroke severity. Curr Neurovasc Res. 2012;9:128-32.

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